Department of Neurology, Klinikum der Ludwig-Maximilians-Universität München, Munich, Germany: Prof. Dr. med. Johannes Levin

German Center for Neurodegenerative Diseases e. V. (DZNE) Munich, Germany: Prof. Dr. med. Johannes Levin

Munich Cluster of Systems Neurology (SyNergy): Prof. Dr. med. Johannes Levin

Department of Psychiatry, Psychotherapy, and Psychosomatics, Faculty of Medicine, University of Augsburg, District Hospital Augsburg, Germany: Prof. Dr. med. Alkomiet Hasan

Department of Gynecology and Obstetrics, Klinikum der Ludwig-Maximilians-Universität München, Munich, Germany: Dr. med. Irene Alba Alejandre

Hamburg Epilepsy Center, Protestant Hospital Alsterdorf, Department of Neurology and Epileptology, Hamburg, Germany: Dr. med. Irene Lorenzi

KBO Kinderzentrum München and Department of Sociopaediatrics at Munich Technical University (TMU), Munich, Germany: Prof. Dr. med. Volker Mall

Division of Pediatric Endocrinology, University Children's Hospital, Saarland University Medical Center, Homburg, Germany.: Prof. Dr. med. Tilman Rohrer

Continuing Medical Education

Diseases Affecting Middle-Aged and Elderly Individuals With Trisomy 21

by Johannes Levin, Alkomiet Hasan, Irene Alba Alejandre, Irene Lorenzi, Volker Mall, and Tilman R. Rohrer

Summary

Background: The life expectancy of individuals with trisomy 21 (Down syndrome, DS) has risen to more than 60 years over the past few decades. As a result, diseases arising in mid and later life have become an issue of major concern in the care of individuals with DS. This article discusses and summarizes, from a multidisciplinary perspective, the diseases commonly affecting this population.

Methods: This narrative review is based on publications identified by a selective literature search, extrapolation of the available evidence, and the authors' personal experience.

Results: Robust epidemiological evidence indicates that many different diseases, which are dealt with by many different medical specialties, are more common in individuals with DS. The genetic background of some of these diseases is now understood down to the molecular level, e.g., primary hypothyroidism or Alzheimer's disease in DS. Recent gains in epidemiological and pathophysiological understanding contrast with a dearth of evidence on treatment for most of these disorders.

Conclusion: In view of the complexity of DS-associated morbidity, it would be desirable for DS-specific multidisciplinary care to be made available to patients with DS.

Cite this as:
Levin J, Hasan A, Alba Alejandre I, Lorenzi I, Mall V, Rohrer TR:
Diseases affecting middle-aged and elderly individuals with trisomy 21. Dtsch Arztebl Int 2023; 120: 14–24.
DOI: 10.3238/arztebl.m2022.0371

Trisomy 21, the most common human chromosomal aberration, is present in approximately 1 in 800 births worldwide. The syndrome is said to have been first described in 1866 by the English physician John Langdon Down (1), although it only received the name "Down syndrome" in 1959 (2). It is usually the result of meiotic nondisjunction, leading to the presence of an extra chromosome 21 in all cells. Translocations and genetic mosaics arising at later stages of embryogenesis are less common and may be associated with milder clinical manifestations (3). Of the approximately 225 genes on chromosome 21, the so-called Down-defining sequences give rise to the clinical manifestations of the syndrome. Introns encoded on chromosome 21 are also thought to play a role in DS-associated disorders (4).

Approximately 50 000 persons with DS now live in Germany. The life expectancy at birth of persons with DS has steadily risen in recent decades: it was 9 years at the turn of the 20th century, and still only 30–35 years in 1970, but persons with DS now regularly live at least to age 60 owing to medical progress, e.g., in the treatment of congenital heart defects (5). This welcome development has increasingly focused

Prevalence

Trisomy 21, the most common human chromosomal aberration, is present in approximately 1 in 800 births worldwide.

The life expectancy of persons with Down syndrome

The life expectancy at birth of persons with DS was 9 years at the turn of the 20th century, and still only 30–35 years in 1970, but persons with DS now regularly live at least to age 60 owing to medical progress, e.g., in the treatment of congenital heart defects.

attention on diseases that persons with DS develop in adulthood. They display accelerated aging and special predispositions for a wide variety of diseases *(Figure 1)* (6).

Learning goals

This article is intended to enable readers to:

- become acquainted with the broad spectrum of disorders that affect people with trisomy 21 in middle age and beyond;
- gain an overview of the diagnostic and therapeutic methods, while bearing in mind the level of evidence that supports them; and
- know the molecular basis of certain disorders that are clearly linked to genes on chromosome 21, to the extent that these are known.

Methods

As this is a broad, multidisciplinary subject, a selective search of the literature from 1959 was carried out in PubMed on the basis of the authors' scientific and clinical experience, and information on certain topics was extrapolated from the available evidence relating to the general population. All types of articles were included. This approach may have led to unintended limitations regarding the selection of the literature.

Results

The role of the family, transition, and care

The family is a major resilience factor for persons with DS, with important effects on their developmental opportunities and socialization. The family is a key enabler of psychosocial integration, as well as basic care, from birth to adulthood. Aside from the morbidity due to trisomy 21 itself, family factors significantly affect the quality of life of persons with DS (7, 8). General educational aspects and family lifestyle play an important role in this regard. For example, children and adolescents whose parents have an active lifestyle display better mobility than those of sedentary parents (9). As persons with DS grow older, they face multiple challenges with respect to their medical care and further life planning; decisions in these matters should be made with the participation of the affected individual, and not just by others caring for him or her. High demands are thus placed on the medical counseling of persons with DS, as well as on their psychosocial and legal support. Siblings often have a special role to play here, and they indeed often carry out their duties admirably. In Germany, the Guardianship and Care Law that went into effect on 1 January 2023 has reinforced the right to self-determination of persons with DS and other conditions.

Somatic and mental illnesses in persons with DS often require highly specialized treatment in centers that are equipped to meet their specific needs, aside from providing high-quality general medical care. In general, these patients should be able, as they grow older, to make a transition from care in social pediatric centers to care in interdisciplinary medical centers for adults with disabilities (for Germany, see www.bagmzeb.de). Although France and Spain now have dedicated units for the interdisciplinary medical care of persons with DS, such units in Germany are scarce, and to date only for children.

Alzheimer's dementia in Down syndrome (DS-AD)

Alzheimer's dementia (AD) has become the most common cause of death in persons with DS (10). The 90% lifetime risk for DS-AD is thought to result from the amyloid precursor protein (APP) being encoded on chromosome 21. An isolated triplication of the APP gene that has been described in some euploid individuals (i.e., persons who do not have trisomy 21) causes autosomal dominant AD with complete penetrance and symptom onset around age 50 (11). The presence of four copies of the APP gene is associated with an even earlier onset of Alzheimer's disease (12), and there is thus a clear gene-dose effect. The pathophysiologic mechanism is that the gene-dose-related overexpression of APP leads to accumulation of the cleavage product amyloid-β (Aβ), which is the major component of AD plaques. Accordingly, DS-AD is considered a form of genetically based AD (11) *(Figure 2)*. Like the isolated multiplication of the APP gene in familial AD, its triplication in persons with DS often causes amyloid angiopathy as well as AD pathology (12, 13). DS-AD is one of the main medical problems in people with DS from their fifth decade onward.

The diagnosis of DS-AD is challenging in several respects. Its clinical presentation is variable and often nonspecific, so that behavioral changes, rather than memory impairment, are often the most prominent manifestations of the condition. Moreover, the baseline cognitive level of persons with DS is highly variable, so standardized tests can be used only with difficulty to identify a decline in cognitive abilities that manifests itself on a first examination. It may thus be useful for all persons with DS to undergo a determination of their baseline cognitive state as

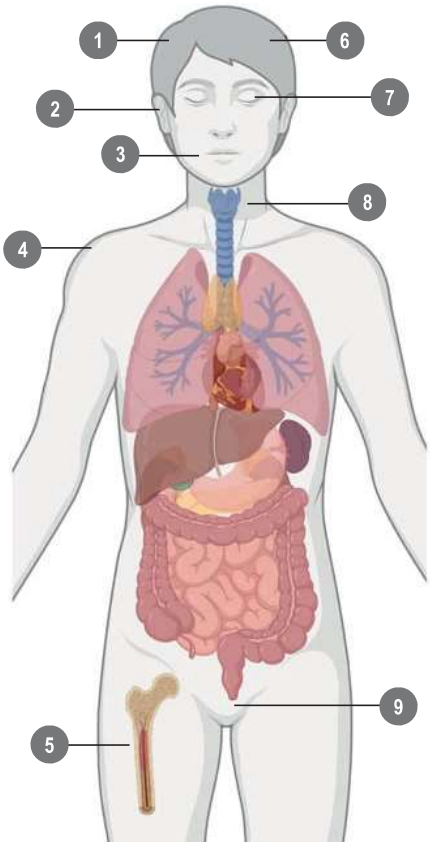
The role of the family, transition, and care

The family is a major resilience factor for persons with DS, with important effects on their developmental opportunities and socialization. The family is a key enabler of psychosocial integration, as well as basic care, from birth to adulthood.

Alzheimer's disease in persons with Down syndrome

Alzheimer's dementia (AD) has become the most common cause of death in persons with DS. The 90% lifetime risk for DS-AD is thought to result from the amyloid precursor protein (APP) being encoded on chromosome 21.

FIGURE 1



Overview of common diseases in adults with Down syndrome

Persons with Down syndrome are at increased risk for a variety of diseases. While cardiovascular events and solid tumors are less common in adults with DS than in the general population, autoimmune, dermatological, and ear, nose and throat diseases, among others, are much more common, as is genetically determined Alzheimer's disease. Because of their importance, childhood hemato-oncological and cardiac diseases are also mentioned in this overview. The following references were used to create the Figure: Refs. 6, 12, 16, 18, 19, 20, 23, 25, 28, 31, 32, 35, 37, e17-e27.

soon as they complete their cognitive development (e.g., with instruments such as the CAMDEX-DS or DTIM) (14,15). Much progress has been made in the use of biomarkers to objectify AD pathology with the amyloid/tau/neurodegeneration (ATN) classification, as well as in repeated neuropsychological assessment with appropriate tests (14). More invasive diagnostic procedures, such as CSF examination and nuclear medical studies, have also shown high validity for the diagnosis of AD in persons with DS, are well tolerated, and have been found useful not only in clinical studies, but also in practice (e.g., in Spain). In the present authors' experience, however, caregivers in Germany are often very reluctant to use such procedures, and hopes for future improvement in diagnosis are centered, rather, on new blood-based biomarkers of DS-AD (14). Biomarkers should always be used, if possible, in view of the wide range of other conditions in the differential diagnosis of DS-AD that can impair cognition and alter behavior (14); these include, for example, hypothyroidism and other general medical diseases, visual and hearing impairment due to senile cataract and presbycusis occurring relatively early in the $4^{th}/5^{th}$ decade, sleep disorders (e.g., sleep apnea), and regression syndrome (URDS: unexplained regression in Down

Common comorbidities

Cardiovascular events and solid tumors are less common in adults with Down syndrome than in the general population, but genetically determined Alzheimer's disease is much more common, as are many other conditions, including autoimmune, dermatologic, and otorhinolaryngeal diseases.

The diagnosis of Alzheimer's disease in persons with Down syndrome

Invasive diagnostic procedures, such as CSF examination and nuclear medical studies, have shown high validity for the diagnosis of AD in persons with DS and are well tolerated.

syndrome)—which, however, occurs mainly in childhood and adolescence, and thus long before DS-AD (16, 22).

The available evidence on the treatment of DS-AD is very sparse, as is the evidence on the treatment of persons with DS in general. A Cochrane review of pharmacotherapy for progressive cognitive impairment in persons with DS found that donepezil displayed a trend toward improved cognitive function (as measured by the Severe Impairment Battery), while memantine was ineffective (17); yet most of the underlying studies were in young persons with DS, some of whom were clearly not demented. We think the main usable data from these studies relate to drug safety: donepezil was found to have more side effects. Thus, our subjective impression that AD drugs are at least partially effective in DS-AD is not currently supported by the scientific evidence. However, the reported trend toward efficacy does, in our view, justify the trial use of donepezil after meticulous individual assessments of the benefits and risks. There are no data on the acetylcholine esterase inhibitors galantamine and rivastigmine, and the available data on memantine do not permit any statement about efficacy. Supportive therapies and socio-medical care remain the core of treatment for persons with DS-AD *(eTable 1)*.

Epilepsy

Epilepsy is very common in persons with DS (prevalence 8–26%), with a first peak in childhood and a second one in the fifth and sixth decades. Persons with DS can have either focal or generalized epilepsy. The etiology may involve neurodegenerative, vascular, and /or metabolic processes, and a disturbance of cortico-thalamic circuits is relevant to the pathogenesis. The most common type of epilepsy in adults with DS is a special form called LOMEDS, "late-onset myoclonic epilepsy in Down syndrome," which is strongly associated with AD pathology (prevalence 41.2–75%); LOMEDS usually arises a few months after the onset of dementia (18). Its phenotype involves single or serial, sometimes severe, bouts of myoclonus and generalized tonic-clonic seizures. The seizures often become more frequent as DS-AD progresses.

Epilepsy in persons with DS is treated analogously to epilepsy in persons without DS, the major distinction remaining that between focal and generalized epilepsy. Particular attention must be paid, however, to the comorbidities of persons with DS, as well as to LOMEDS as a special form of epilepsy in this population. In LOMEDS, benefit has been shown empirically from the use of levetiracetam to treat myoclonus and generalized convulsive seizures (alternatively: valproate, at low doses because of the multimorbidity of persons with DS and the risk of valproate encephalopathy). In principle, drugs that are mainly sodium-channel blockers (oxcarbazepine, carbamazepine, eslicarbazepine, phenytoin) can worsen myoclonus (18, 19). On the other hand, we consider lamotrigine a good option because it is usually well tolerated, as long as myoclonus is not the main problem to be treated *(eTable 1)*.

Sleep-related disorders

Sleep-related disorders are common in persons with DS and can cause daytime sleepiness, impaired concentration, and behavioral abnormalities. Obstructive sleep apnea (OSA) is the most common sleep disorder in these persons because of their specific anatomical and physiological characteristics (small oropharynx, adenotonsillar hyperplasia, hypotonia, obesity). The most common symptoms of OSA are pauses in breathing, mouth-breathing during sleep, snoring, night-time awakening, dry mouth, and sleeping with the head in reclination. OSA is diagnosed by polygraphy or polysomnography and affects more than 65% of adults with DS (19). It improves with CPAP treatment. DS patients are generally well able to tolerate both diagnostic testing by polysomnography and CPAP treatment (19). Other sleep disorders are treated with measures to promote proper sleep hygiene (19).

Mental illnesses

The mental health of persons with DS unfortunately receives little attention. For example, a major review only mentions the topic in passing (6). In current overview, prevalence rates of mental illness in this population were derived from a comprehensive cohort of 30 326 control subjects and 6078 persons with DS (ages 0–89 years) (20). Increased prevalences were found in the following diagnostic categories: anxiety disorders (odds ratio [OR]: 1.09), obsessive-compulsive disorders (OR: 20.15), affective disorders (OR: 3.41) (especially unipolar depression, OR: 1.27), psychotic disorders (any) (OR: 3.87), schizophrenia (OR: 1.87), tic disorders (OR: 1.67), impulse-control disorders (OR: 23.03), and dementing diseases (OR: 66.97). Low prevalences were found for bipolar disorder, post-traumatic stress disorder, and dependence

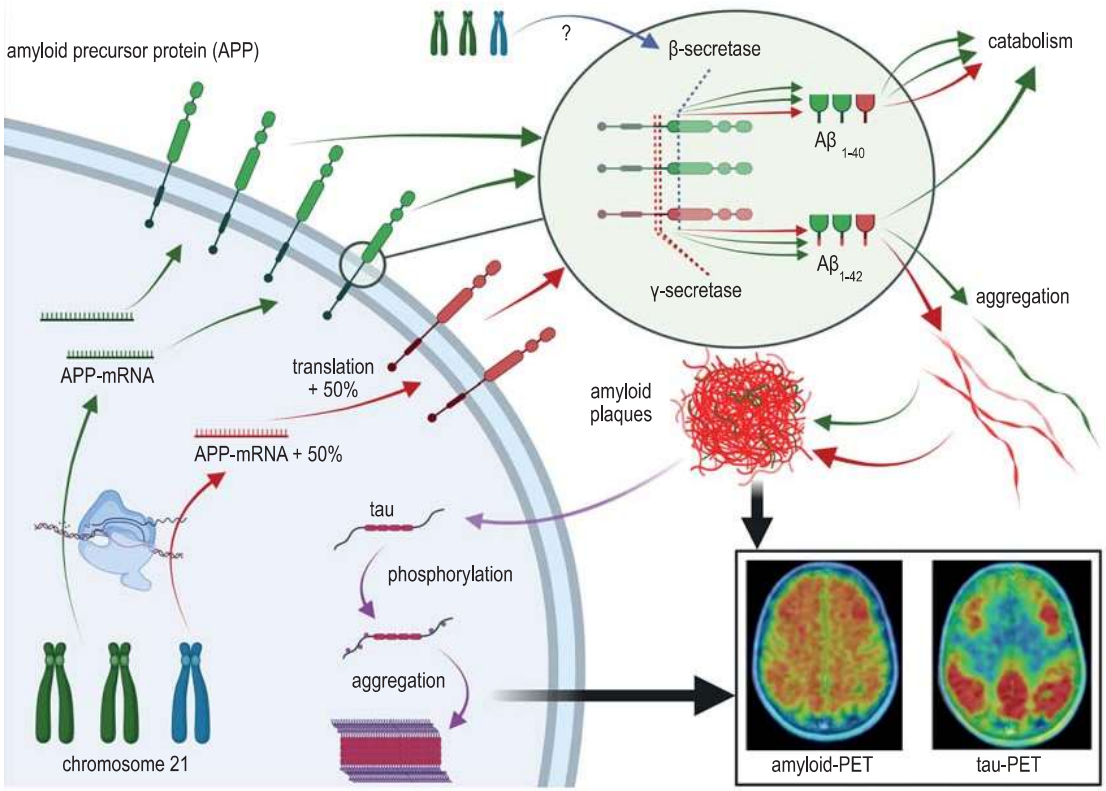
Epilepsy

Epilepsy is very common in persons with DS (prevalence 8–26%), with a first peak in childhood and a second one in the fifth and sixth decades.

Sleep-related disorders

Sleep-related disorders are common in persons with DS and can cause daytime sleepiness, impaired concentration, and behavioral abnormalities. Obstructive sleep apnea is the most common sleep disorder in these persons because of their specific anatomical and physiological characteristics.

FIGURE 2



The pathophysiology of Alzheimer's disease in Down syndrome

The presence of a third copy of the amyloid precursor protein (APP) gene leads to an approximately 50% increase in transcription and translation of the protein. Accordingly, more APP degradation products are produced. As a product of the imprecise limited proteolysis by gamma-secretase, two different cleavage products are formed: amyloid-β $(Aβ)_{1–40}$ and $Aβ_{1–42}$. The highly amyloidogenic cleavage product, $Aβ_{1–42}$, present in increased amounts, can no longer be broken down adequately, so that Alzheimer's plaques may form in the brain as early as the 2nd decade. The amyloid cascade leads to intraneuronal hyperphosphorylation and fibril formation of the tau protein, which in turn causes cell damage. The role of other genetic factors, such as the increased amount of β-secretase, which is also encoded on chromosome 21, and the role of epigenetic factors remain poorly understood.

disorders, among others (20). The data on attention deficit—hyperactivity disorder and eating disorders are less clear. It follows that, whenever a mental illness is suspected in an adult with DS, the main emphasis should be on anxiety disorders in general, psychotic disorders, obsessive-compulsive disorders, and affective disorders, mainly unipolar depression. Attention should also be paid to the persistence of childhood developmental disorders (especially autism spectrum disorders) or tic disorders into adulthood. The ICD-10 criteria must be sought, even though, in everyday clinical practice, these often do not suffice for the diagnosis of mental illness in persons with DS. Clinical experience and an appreciation of the particular aspects of mental illness in this patient population *(eTable 2)* play an important role. The Diagnostic Manual – Intellectual Disability (DM-Id-2) can be used to facilitate identification of the correct diagnosis. No validated scales are available for this population. Somatic comorbidities that might explain the apparently psychiatric symptoms (e.g., hypothyroidism, obstructive sleep apnea, epilepsy) should always be ruled out.

Mental illness

Increased prevalences were found for anxiety disorders, obsessive-compulsive disorders, affective disorders (especially unipolar depression), psychotic disorders, schizophrenia, tic disorders, impulse-control disorders, and dementing diseases.

The diagnostic focus

Whenever a mental illness is suspected in an adult with DS, the main emphasis should be on anxiety disorders in general, psychotic disorders, obsessive-compulsive disorders, and affective disorders, mainly unipolar depression.

In the absence of studies on specific interventions, systematic reviews, or meta-analyses, therapeutic recommendations can only be extrapolated from the non-Down syndrome population. A narrative review presents the therapeutic options, while stressing the need for special attention to the adverse effects of psychotropic drugs (including QTc changes, weight gain, constipation, and sedation) in persons with DS (21). Caution is recommended in the use of drugs associated with relevant QTc disturbances (e.g., escitalopram, amisulpride), proconvulsant properties (e.g., bupropion, clozapine), marked metabolic effects (e.g., mirtazapine, olanzapine, quetiapine), marked effects on prolactin levels (e.g., paliperidone, amisulpride), and potential dyscognitive effects (e.g., tricyclic antidepressants and antipsychotic drugs that are strong D2R blockers). Combinations of such drugs, in particular, require critical evaluation. The indications for such drugs in this population are generally off-label. Specific studies of psychotherapy and psychosocial therapies in this population are not available, either; with regard to these as well, the treatment of DS patients is based the guidelines for the general population, with due attention to possible impairments of sensation, cognition, and language *(eTable 2)*. Important elements of psychotherapy for patients with DS, including adults, are variation in the treatment setting, the inclusion of play, involvement of caregivers (family members and others), a generous time investment compared to the psychotherapy of persons who do not have DS, and working with the patient's family.

Somatic diseases

Persons with DS suffer from a variety of endocrinologic, metabolic, gastrointestinal, and autoimmune disorders *(Table)*. A few important entities will be discussed in what follows.

Hypothyroidism

Hypothyroidism affects 39% (18–29 years) to 51% (>30 years) of persons with DS and often has a nonspecific presentation (23). It occurs together with pernicious anemia in 0–11% cases, and it is associated with an earlier onset of DS-AD (under age 47) (24). Thyroid hormone levels and thyroid antibodies should be checked annually to detect this condition. Treatment is started after a TSH level has been determined; we generally give L-thyroxine at a dose of 1–2 µg/kg body weight per day.

Hyperthyroidism is also more common than in the general population (0.65%) and presents with weight loss, restlessness, tremor, and heat intolerance (25). Endocrinologic consultation and treatment with beta-blockers and thyrostatic agents are recommended.

Obesity

Obesity is common, complicated, and associated with other comorbidities such as obstructive sleep apnea, diabetes, and orthopedic and cardiopulmonary problems. 25% of children and 50% of adult persons with DS are obese (6). The BMI should be determined annually. Weight stabilization and weight loss can be achieved with exercise, as well as diet management, portion control, and consistent mealtimes. Diet and exercise studies have not shown any improvement of cardiovascular risks, but they have revealed a better quality of life and increased participation in activities (26, 27).

Osteoporosis

The reported prevalences of osteopenia, osteoporosis, and osteoporotic fractures (1.4% - 45.1%) are derived from only six small-scale studies with a total of 796 patients. Special problems in this patient group include the necessary correction of bone densitometry (DEXA) for short stature and the diminished amount of new bone formation in the face of excessive bone resorption. These aspects make bisphosphonate treatment seem questionable. If a person with DS sustains a pathological fracture, a secondary cause of osteoporosis should be sought, e.g., hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, or a drug side effect (26).

Diabetes mellitus

A British study with 6430 subjects showed a higher prevalence of diabetes in adults with DS than in the general population (23). The risk of type 1 diabetes mellitus (T1DM) is significantly higher because of more prevalent autoimmune disease, while the risk of type 2 diabetes (T2DM) is lower (28).

Gastroenterological diseases

Dysphagia affects 25% of persons with DS and becomes more common with age. Signs of aspiration, such as coughing, throat-clearing during meals, weight loss, and behavioral changes, should be evaluated with suitable x-ray studies and a speech therapy assessment (29). Celiac disease can arise at any stage of life (overall prevalence, 7–17%) (28); it may be asymptomatic or present nonspecifically with symptoms such as behavioral or mood changes, weight loss, and/or diarrhea. It is suggested in the current recommendations that adults with DS should be screened for symptomatic celiac disease, and that children should be screened every three years as part of their routine care. The only known effective treatment is a strict gluten-free diet (29).

Obesity

25% of children and 50% of adult persons with DS are obese. Weight stabilization and weight loss can be achieved with exercise, as well as diet management, portion control, and consistent mealtimes.

Diabetes mellitus

The risk of type 1 diabetes mellitus (T1DM) is significantly higher because of more prevalent autoimmune disease; the risk of type 2 diabetes (T2DM) is lower.

TABLE

Somatic diseases in persons with Down syndrome

Etiology / connection with chromosome 21	Clinical syndrome	Diagnostic evaluation	Symptomatic treatment
Hypothyroidism			
Dyrk1a gene located on chromosome 21q22.2	• obesity • fatigue • reduced performance • pale, pasty skin	laboratory tests for thyroid-stimulating hormone, free triiodothyronine; free thyroxine, thyroperoxidase antibodies	daily administration of L-thyroxine 1.5–2 µg/kg body weight evidence level 1 recommendation grade A (e10)
Osteoporosis			
• occurs in 1.4–45.1% of persons with Down syndrome • causes include limited mobility, antiepileptic and psychotropic drugs, nutritional status, vitamin D deficiency, and celiac disease	• vertebral compression fractures • pathological fractures	bone densitometry from age 50 onward, or from menopause onward	The efficacy of calcium, vitamin D, and bisphosphonate in people with Down syndrome is questionable. evidence level 1 recommendation grade 0 (26, e9)
Diabetes			
• type 1 diabetes; increased prevalence of autoimmune disease • type 2 diabetes: obesity	• type 1 diabetes: polyuria, polydipsia • type 1 diabetes + type 2 diabetes: fatigue	• type 1 diabetes: – HbA_{1c} – blood sugar – blood gas analysis – diabetes-specific antibodies • type 2 diabetes: – HbA_{1c} every 3 years	• type 1 diabetes: – diet, insulin, evidence level 1 recommendation grade A • type 2 diabetes: – diet – metformin – SGLT2 inhibitors – GLP-1 receptor agonists – sulfonylurea – insulin steps and combinations: cf. national care guideline for type 2 diabetes (e11)
Cardiology			
• mitral valve prolapse in up to 5 % of persons with Down syndrome • aortic valve insufficiency • mitral valve insufficiency • pulmonary arterial hypertension Persons with DS born from the 1950s to the 1980s have high rates of Eisenmenger reactions due to the lower rates of corrective surgery (30).	• manifestations of: – congestive heart failure – dyspnea – orthopnea – pulmonary rales – lower limb edema – superior vena cava syndrome A heart murmur may be absent!	• echocardiography • proBNP	cardiological follow-up (29) cf. the current guidelines of the German Cardiological Society on congestive heart failure and pulmonary arterial hypertension (e12, e13)
Pulmonology, infectious disease			
• the second most common cause of death in persons with Down Syndrome because of the weak immune system • midface hypoplasia • muscle hypotonia • obstructive sleep apnea syndrome • narrow upper airways • relative macroglossia • gastroesophageal reflux • recurrent aspiration	also atypical, silent aspiration	• physical examination • laboratory tests • imaging (chest x-ray)	antibiotic and antiviral treatment evidence level 1, recommendation grade B (e14, e15) prevention: annual influenza vaccination; a COVID-19 booster and Pneumovax booster (29, 33)
Obesity			
• obstructive sleep apnea syndrome • reduced control over appetite and satiety • reduced physical activity • hypothyroidism	elevated body mass index	measurement of height and weight	more exercise, including: swimming, dancing, personal trainer; diet management, portion control, consistent mealtimes evidence level 1 recommendation grade 0 (e16)

Evidence level 1 = randomized, controlled trial(s); 2 = case-control study (studies); 3 = non-analytic case study (studies); 4 = expert opinion
Recommendation grade A = strong recommendation (must); B = recommendation (should); 0 = open recommendation (may)
EL, evidence level; RG, recommendation grade

Heart diseases

40–50% of persons with DS have a congenital heart defect (29). Among babies born from the 1950s and 60s to the 1980s, only 0.0–2.1% of congenital heart defects were surgically corrected, and 18.3–53.3% of these children developed an Eisenmenger reaction (irreversibly fixed pulmonary hypertension, leading to shunt reversal). It was only in the 1990s and 2000s that this figure dropped to 1.7–0.5% (30). The Eisenmenger reaction significantly curtails survival (30, 31). Coronary heart disease, hypertension, and myocardial infarction beyond age 51 are less common than in the general population, while hypotension is more common (23, 29, 32).

Lung diseases, infectious diseases, and COVID-19

Influenza, pneumonia, and aspiration are common, accounting for 25% of the hospital admissions of persons with DS (29). Respiratory infections are the second most common cause of death.

Persons with DS are the only genetic syndromic group with an elevated hospitalization rate and elevated mortality due to COVID-19; these figures lie between those of persons without DS aged 70 to 79 and those over age 80. As a result, persons with DS are given priority for vaccination against COVID (33). They are able to mount an adequate mRNA-induced antibody response (34).

Hematologic diseases and cancer

The risk of leukemia is highest in childhood and remains elevated until age 30. The standardized incidence ratio (SIR) is 13.9 [95% confidence interval: 8.74; 8.5] for lymphocytic leukemias and 11.8 [7.11; 18.5] for myeloid leukemias. The overall risk of solid tumors is lower in persons with DS, especially the lifetime risk of lung cancer, breast cancer, and cervical cancer. This is thought to be related, in part, to an anti-angiogenesis gene encoded on chromosome 21. Testicular cancer is three times as common as in the general male population, possibly because of the higher frequency of cryptorchidism (35). Cancer plays a relatively minor role among the health problems of adults with DS.

Gynecologic preventive care, fertility, and menopause

Menstrual disorders and gynecological preventive care

In some respects, the gynecologic aspects of girls and women with DS are no different than in the general population, including the age of menarche, menstrual cycles, internal and external genitalia, and sex hormone profiles. Nonetheless, issues of menstrual hygiene, premenstrual disorders, and contraception are often more difficult to address in girls and women with DS who suffer from cognitive deficits (36). Comorbidities that are common in persons with DS (e.g., hypothyroidism, epilepsy, obesity), and the medications used to treat these comorbidities, can cause menstrual irregularity, amenorrhea, or abnormal uterine bleeding. Nevertheless, women with DS undergo gynecologic preventive care less frequently than recommended, in contrast to other types of medical treatment and preventive care. Improvement is needed, particularly with regard to screening for cervical cancer in sexually active women with DS, and also with regard to breast cancer screening (37).

Fertility

Women with DS are fertile and can become pregnant. In contrast, nearly all men with DS are infertile, probably because of impaired spermatogenesis and primary gonadal insufficiency. Nonetheless, rare cases of children born to fathers with DS have been reported (38). The probability that children of persons with DS will also have DS is approximately 50% (39). Girls with DS, in particular, should be educated about sexuality, healthy relationships, and birth control. More generally, according to the recommendations of the National Down Syndrome Society of the United States (www.ndss.org), the goal of social and sexual education should be to help persons with DS develop a healthy and positive social and sexual awareness and thus become able to make personal choices that enhance their overall happiness and quality of life.

Early menopause

Menopause begins an average of six years earlier in women with DS than in the general population (45 versus 51 years) (37). Among women with DS, early menopause has been linked to an earlier age of onset of AD (40).

Low levels of endogenous bioavailable estradiol in postmenopausal women with DS are associated with an earlier onset of dementia and a higher overall risk of dementia. A higher body-mass index is associated with elevated serum estradiol and estrogen levels. Among postmenopausal women with DS, obese women performed markedly better than nonobese women on verbal memory tests and on a general test of neuropsychological function. Moreover, men with DS develop DS-AD earlier than women with DS. There have not yet been

Cancer

The risk of leukemia is highest in childhood and remains elevated until age 30. Testicular cancer is three times as common as in the general male population.

Fertility

Women with DS are fertile and can become pregnant, but nearly all men with DS are infertile, probably because of impaired spermatogenesis and primary gonadal insufficiency.

any published clinical trials of estrogen or hormone replacement therapy in women with Down syndrome.

Overview

Owing to the better medical care that persons with DS now receive as children, and their consequently increased life expectancy, diseases of middle-aged and elderly persons with DS have attained a new prominence. High-quality epidemiological research has clearly revealed associations between DS and a variety of diseases, some of which have been elucidated down to the molecular level. As far as the treatment of comorbid disorders is concerned, adequate evidence for the DS population is generally lacking, and recommendations are extrapolated from the evidence for well-evaluated treatment methods in the general population. This dearth of evidence makes it impossible, in many situations, to satisfy the requirement stated in the UN Convention on the Rights of Persons with Disabilities for medical treatment of an equivalent standard based on up-to-date knowledge. Properly implementing the UN Disability Rights Charter will require markedly stepped-up efforts in this area, particularly as concerns interventional trials for diseases that are well understood at the molecular level, such as DS-AD (e1). On the whole, this vulnerable population stands to benefit from the consistent provision of structured, specialized, and interdisciplinary treatment.

Acknowledgments

We thank Dr. med. Georg Nübling for critically reviewing the article and preparing the Figures, and Prof. Dr. med. Jan Remi for critically reviewing the article.

Conflict of interest statement

Prof. Levin reports that he has received lecture honoraria from Bayer Vital, Biogen, and Roche; consultant's fees from Axon Neuroscience and Biogen; and author's fees from Thieme (Medizinverlag) and W. Kohlhammer GmbH (Medizinverlag). He also reports being paid for his work as Chief Medical Officer of MODAG GmbH and as an inventor in a patent filed by MODAG GmbH entitled "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8).

Prof. Hasan is editor of the AWMF S3 guideline on schizophrenia and has received lecture honoraria from Recordati, Janssen, Lundbeck and Otsuka; he has served on advisory boards for these companies and for Rovi. He receives research funding from the BMBF, DFG, and GBA Innovation Fund. He receives author's fees as editor of InFo Neurologie & Psychiatrie, a Springer publication.

Prof. Rohrer has received lecture honoraria from RG, Alexion, BioMarin, Novo Nordisk, and Merck; consultant's fees from Alexion, BioMarin, Novo Nordisk, Merck, and Pfizer; research funding from BMG, BMBF, Novo Nordisk, and Merck; and author's fees from Thieme (Medizinverlag).

Dr. Alba Alejandre, Dr. Lorenzi, and Prof. Mall state that they have no conflict of interest.

Manuscript received on 24 May 2022, revised version accepted on 11 March 2022.

Translated from the original German by Ethan Taub, M.D.

References

1. Down JL: Observations on an ethnic classification of idiots. 1866. Ment Retard 1995; 33: 54–6.
2. Lejeune J, Turpin R, Gautier M: [Mongolism; a chromosomal disease (trisomy)]. Bull Acad Natl Med 1959; 143: 256–65.
3. Nuebling GS, Prix C, Brendel M, et al.: Low-degree trisomy 21 mosaicism promotes early-onset Alzheimer disease. Neurobiol Aging 2021; 103: 147.e1–e5.
4. Coppede F: The genetics of folate metabolism and maternal risk of birth of a child with Down syndrome and associated congenital heart defects. Front Genet 2015; 6: 223.
5. Glasson EJ, Dye DE, Bittles AH: The triple challenges associated with age-related comorbidities in Down syndrome. J Intellect Disabil Res 2014; 58: 393–8.
6. Bull MJ: Down syndrome. N Engl J Med 2020; 382: 2344–52.
7. Lee A, Knafl K, Van Riper M: Family variables and quality of life in children with Down syndrome: a scoping review. Int J Environ Res Public Health 2021; 18: 419.
8. Capone G, Goyal P, Ares W, Lannigan E: Neurobehavioral disorders in children, adolescents, and young adults with Down syndrome. Am J Med Genet C Semin Med Genet 2006; 142C: 158–72.
9. Sollerhed AC, Hedov G: Active parents—active children—a study among families with children and adolescents with Down syndrome. Int J Environ Res Public Health 2021; 18: 660.
10. Coppus AM, Evenhuis HM, Verberne GJ, et al.: Survival in elderly persons with Down syndrome. J Am Geriatr Soc 2008; 56: 2311–6.
11. Wiseman FK, Al-Janabi T, Hardy J, et al.: A genetic cause of alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci 2015; 16: 564–74.
12. Grangeon L, Cassinari K, Rousseau S, et al.: Early-onset cerebral amyloid angiopathy and alzheimer disease related to an APP locus triplication. Neurol Genet 2021; 7: e609.
13. Carmona-Iragui M, Videla L, Lleo A, Fortea J: Down syndrome, alzheimer disease, and cerebral amyloid angiopathy: the complex triangle of brain amyloidosis. Dev Neurobiol 2019; 79: 716–37.
14. Nubling G, Wagemann O, Loosli SV, Wlasich E, Danek A, Levin J: [Diagnosing alzheimer dementia in people with Down syndrome in accordance with ICD, DSM V and A/T/N system]. Fortschr Neurol Psychiatr 2022; 90: 416–20.
15. Kuske B, Wolff C, Govert U, Muller SV: Early detection of dementia in people with an intellectual disability—a German pilot study. J Appl Res Intellect Disabil 2017; 30 (Suppl 1): 49–57.
16. Wagemann O, Loosli SV, Voglein J, et al.: [Regression in young adults with Down-syndrome: a case series]. Fortschr Neurol Psychiatr 2022; 90: 465–47.
17. Livingstone N, Hanratty J, McShane R, Macdonald G: Pharmacological interventions for cognitive decline in people with Down syndrome. Cochrane Database Syst Rev 2015; 2015: CD011546.
18. Altuna M, Gimenez S, Fortea J: Epilepsy in Down syndrome: a highly prevalent comorbidity. J Clin Med 2021; 10: 2776.
19. Gimenez S, Altuna M, Blessing E, Osorio RM, Fortea J: Sleep disorders in adults with Down syndrome. J Clin Med 2021; 10: 3012.
20. Rivelli A, Fitzpatrick V, Chaudhari S, et al.: Prevalence of mental health conditions among 6078 individuals with Down syndrome in the United States. J Patient Cent Res Rev 2022; 9: 58–63.
21. Palumbo ML, McDougle CJ: Pharmacotherapy of Down syndrome. Expert Opin Pharmacother 2018; 19: 1875–89.
22. Santoro SL, Baumer NT, Cornacchia M, et al.: Unexplained regression in Down syndrome: management of 51 patients in an international patient database. Am J Med Genet A 2022; 188: 3049–62.
23. Alexander M, Petri H, Ding Y, Wandel C, Khwaja O, Foskett N: Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. Dev Med Child Neurol 2016; 58: 246–54.
24. Lai F, Mercaldo ND, Wang CM, Hersch MS, Hersch GG, Rosas HD: Association between hypothyroidism onset and alzheimer disease onset in adults with Down syndrome. Brain Sci 2021; 11: 1223.

Menopause

Among women with Down syndrome, early menopause has been linked to an earlier age of onset of Alzheimer's disease.

25. Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM, Cano-Perez JF: Hyperthyroidism in a population with Down syndrome (DS). Clin Endocrinol (Oxf) 2009; 71: 110–4.
26. Tsou AY, Bulova P, Capone G, et al.: Medical care of adults with Down syndrome: a clinical guideline. JAMA 2020; 324: 1543–56.
27. Hardee JP, Fetters L: The effect of exercise intervention on daily life activities and social participation in individuals with Down syndrome: a systematic review. Res Dev Disabil 2017; 62: 81–103.
28. Rivelli A, Fitzpatrick V, Wales D, et al.: Prevalence of endocrine disorders among 6078 individuals with Down syndrome in the United States. J Patient Cent Res Rev 2022; 9: 70–4.
29. Jensen KM, Bulova PD: Managing the care of adults with Down's syndrome. BMJ 2014; 349: g5596.
30. Korten MA, Helm PC, Abdul-Khaliq H, et al.: Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease. Heart 2016; 102: 1552–7.
31. Dimopoulos K, Kempny A: Patients with Down syndrome and congenital heart disease: survival is improving, but challenges remain. Heart 2016; 102: 1515–7.
32. Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK: Risk of major cardiovascular events in people with Down syndrome. PLoS One 2015; 10: e0137093.
33. Jamela S: Beschluss der STIKO zur 1. Aktualisierung der COVID-19-Impfempfehlung. Berlin: Robert Koch-Institut 2021; p. 33–43.
34. Esparcia-Pinedo L, Yarci-Carrión A, Mateo-Jiménez G, et al.: Development of an effective immune response in adults with Down syndrome after SARS-CoV-2 vaccination. Clin Infect Dis 2022; ciac590. Online ahead of print.
35. Hasle H, Friedman JM, Olsen JH, Rasmussen SA: Low risk of solid tumors in persons with Down syndrome. Genet Med 2016; 18: 1151–7.
36. Wandresen G, Sgarbi F, Nisihara R: Management of contraceptives and menstrual complaints in patients with Down syndrome. Gynecol Endocrinol 2019; 35: 103–8.
37. Smith AJB, Applebaum J, Tanner EJ, Capone GT: Gynecologic care in women with Down syndrome: findings from a national registry. Obstet Gynecol 2020; 136: 518–23.
38. Pradhan M, Dalal A, Khan F, Agrawal S: Fertility in men with Down syndrome: a case report. Fertil Steril 2006; 86: 1765.1–3.
39. Bovicelli L, Orsini LF, Rizzo N, Montacuti V, Bacchetta M: Reproduction in Down syndrome. Obstet Gynecol 1982; 59: 13–7.
40. Schupf N, Lee JH, Pang D, et al.: Epidemiology of estrogen and dementia in women with Down syndrome. Free Radic Biol Med 2018; 114: 62–8.

Correspondence address
Prof. Dr. med. Johannes Levin
Klinik für Neurologie
Klinikum der Ludwig-Maximilians-Universität München und
Deutsches Zentrum für Neurodegenerative Erkrankungen e. V. (DZNE)
Feodor-Lynen Str. 17, 81377 Munich, Germany
jlevin@med.uni-muenchen.de

Cite this as:
Levin J, Hasan A, Alba Alejandre I, Lorenzi I, Mall V, Rohrer TR: Diseases affecting middle-aged and elderly individuals with trisomy 21: Dtsch Arztebl Int 2023; 120: 14–24. DOI: 10.3238/arztebl.m2022.03711

▶ **Supplementary material**

eReferences, eTables:
www.aerzteblatt-international.de/m2022.0371

Further information on CME

- Participation in the CME certification program is possible only via the Internet: cme.aerzteblatt.de. This unit can be accessed until 8 January 2024. Submissions by letter, e-mail, or fax cannot be considered.
- The completion time for all newly started CME units is 12 months. The results can be accessed 4 weeks following the start of the CME unit. Please note the respective submission deadline at: cme.aerzteblatt.de.
- This article has been certified by the North Rhine Academy for Continuing Medical Education. CME points can be managed using the "uniform CME number" (einheitliche Fortbildungsnummer, EFN). The EFN must be stated during registration on www.aerzteblatt.de ("Mein DÄ") or entered in "Meine Daten", and consent must be given for results to be communicated. The 15-digit EFN can be found on the CME card (8027XXXXXXXXXX).

CME credit for this unit can be obtained via cme.aerzteblatt.de until 8 January 2024.

Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

How has the life expectancy of persons with Down syndrome changed since the 1970s?

a) It has remained stable.
b) It has declined because of mortality due to COVID-19.
c) It has increased to >60 years, mainly because of improvements in the treatment of heart diseases.
d) Because of the protective factors located on chromosome 21, e.g., against solid tumors, persons with DS tend to live longer than those in the general population.
e) Men with Down syndrome have a life expectancy of at least 70 years if they survive to age 10.

Question 2

What is the best characterization of the state of the evidence concerning treatments for diseases associated with Down syndrome?

a) Evidence for the treatment of people with DS is based on expert opinion.
b) Evidence for the treatment of most diseases associated with Down syndrome is incomplete.
c) When Germany signed the UN Convention on the Rights of Persons with Disabilities, the performance of clinical trials on topics related to Down syndrome became obligatory, like the development of drugs exclusively for children. This has led to a marked improvement of the situation.
d) Evidence on treatment that has been derived the general population is directly transferable to people with Down syndrome, so the state of the evidence can generally be considered good.
e) The vast majority of treatment options are rated as evidence level I.

Question 3

What causes Alzheimer's disease in people with Down syndrome?

a) In people with Down syndrome, small traces of aluminum lead to the accumulation of Aβ 1–42 and thus to plaque formation.
b) Epigenetic changes increase the expression of α-secretase, accelerating plaque formation.
c) The tau gene is located on chromosome 21 and is therefore expressed three times more in people with Down syndrome, resulting in increased neurofibril formation.
d) The amyloid precursor protein is located on chromosome 21 and is more highly expressed, promoting plaque formation.
e) γ-secretase is located on chromosome 21 and has an approximately fivefold increased enzymatic activity in trisomy 21.

Question 4

How likely is it that the child of a woman with Down syndrome will also have Down syndrome?

a) 0%
b) 20%
c) 50%
d) 80%
e) 100%

Question 5

What category of mental illness is <u>not</u> more common in adults with trisomy 21 than in the general population?

a) disorders from the schizophrenic spectrum
b) affective disorders
c) psychiatric disorders
d) addictive disorders
e) obsessive-compulsive disorders

Question 6

What internal disease is <u>not</u> more common in persons with trisomy 21 than in the general population?

a) congenital heart disease
b) iron deficiency
c) exocrine pancreatic failure
d) celiac disease
e) hypothyroidism

Question 7

What type of cancer is approximately three times as common in men with Down syndrome, compared to the general population?

a) lung cancer
b) renal cell carcinoma
c) testicular cancer
d) hepatocellular carcinoma
e) pancreatic carcinoma

Question 8

What is the preferred measure to be taken for persons with Down syndrome who suffer from obesity?

a) change to a low-carbohydrate diet
b) placement of a gastric band
c) increased physical activity
d) placement of a gastric bypass
e) drugs to delay fat absorption

Question 9

What drug has been found to be effective against late-onset myoclonic epilespy in Down syndrome (LOMEDS)?

a) levetiracetam
b) clonazepam
c) gabapentin
d) pregabalin
e) rufinamide

Question 10

Which of the following diseases is common in persons with Down syndrome?

a) coronary heart disease
b) ventricular tachycardia
c) mitral valve prolapse
d) atrial flutter
e) Takotsubo syndrome

► **Participation is possible only via the Internet: cme.aerzteblatt.de**

Supplementary material to:

Diseases Affecting Middle-Aged and Elderly Individuals With Trisomy 21

by Johannes Levin, Alkomiet Hasan, Irene Alba Alejandre, Irene Lorenzi, Volker Mall, and Tilman R. Rohrer

Dtsch Arztebl Int 2023; 120: 14–24. DOI: 10.3238/arztebl.m2022.0371

eReferences

e1. Fortea J, Vilaplana E, Carmona-Iragui M, et al.: Clinical and biomarker changes of alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet 2020; 395: 1988–97.

e2. d'Orsi G, Specchio L, Apulian Study Group on Senile Myoclonic Epilepsy.: Progressive myoclonus epilepsy in Down syndrome patients with dementia. J Neurol 2014; 261: 1584–97.

e3. Vignoli A, Zambrelli E, Chiesa V: Epilepsy in adult patients with Down syndrome: a clinical-video EEG study. Epileptic Disord 2011; 13: 125–32.

e4. Thom RP, Palumbo ML, Thompson C, Mc Dougle CJ, Ravichandran CT: Selective serotonin reuptake inhibitors for the treatment of depression in adults with Down syndrome: A preliminary retrospective chart review study. Brain Sci 2021; 11: 1216.

e5. Esbensen AJ, Beebe DW, Byars KC, Hoffmann EK: Use of sleep evaluations and treatments in children with Down Syndrome. J Dev Behav Pediatr 2016; 37: 629–36.

e6. Lunsky Y, Khuu W, Tadrous M, Vigod S, Cobigo V, Gomes T: Antipsychotic use with and without comorbid psychiatric diagnosis among adults with intellectual and developmental disabilities. Can J Psychiatry 2018; 63: 361–9.

e7. Sutor B, Hansen MR, Black JL et al.: Obsessive compulsive disorder treatment in patients with Down syndrome: a case series. Downs Syndr Res Pract 2006; 10: 1–3.

e8. AWMF: S3 Leitlinie Autismus-Spektrum-Stoerungen-Kindes-Jugend-Erwachsenenalter-Therapie. www.awmf.org/uploads/tx_szleitlinien/028–047l_S3_Autismus-Spektrum-Stoerungen-Kindes-Jugend-Erwachsenenalter-Therapie_2021–04_1.pdf (last accessed on 3 November 2022).

e9. AWMF: Leitlinien Detailansicht: Prophylaxe, Diagnostik und Therapie der Osteoporose. www.awmf.org/leitlinien/detail/ll/183–001.html (last accessed on 3 November 2022).

e10. Brent GA, et al., Hypothyroidism and Thyroiditis. In: Melmed S, Polonsky KS, Larsen PR, Kronenbeg HM, editors. Williams textbook of endocrinology, 12th ed. Philadelphia: W.B. Saunders, 2011: 406–39.

e11. AWMF: Nationale VersorgungsLeitlinie (NVL) Typ-2-Diabetes. www.awmf.org/leitlinien/detail/ll/nvl-001.html (last accessed on 3 November 2022).

e12. DGK: Pulmonale Hypertonie. https://leitlinien.dgk.org/stichwort/pulmonale-hypertonie/ (last accessed on 3 November 2022).

e13. DGK: Positionspapier Herzinsuffizienz und Diabetes. https://leitlinien.dgk.org/stichwort/herzinsuffizienz/ (last accessed on 3 November 2022).

e14. AWMF: Leitlinien-Detailansicht. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie. www.awmf.org/leitlinien/detail/ll/020–020.html (last accessed on 3 November 2022).

e15. AWMF: Leitlinien Detailansicht. Epidemiologie, Diagnostik und Therapie erwachsener Patienten mit nosokomialer Pneumonie. www.awmf.org/leitlinien/detail/ll/020–013.html (last accessed on 3 November 2022).

e16. AWMF: Leitlinie Adipositas – Prävention und Therapie. www.awmf.org/leitlinien/detail/ll/050–001.html (last accessed on 3 November 2022).

e17. Pilcher ES: Dental care for the patient with Down syndrome. Down Syndrome Research and Practice 1998; 5: 11–116.

e18. Cheng RHW, Yiu CKY, Leung WK: Oral health in individuals with Down Syndrome. www.intechopen.com/chapters/17991 (last accessed on 3 Novemver 2022).

e19. Carter DM, Jegasothy BV: Alopecia areata and Down syndrome. Arch Dermatol 1976; 112: 1397–9.

e20. Ercis M, Balci S, Atakan N: Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. Clin Genet 1996; 50: 317–20.

e21. McKelvey KD, Fowler TW, Akel NS, et al.: Low bone turnover and low bone density in a cohort of adults with Down syndrome. Osteoporos Int 2013; 4: 1333–8.

e22. Kumar P., Panigrahi I, Sankhyan N, Ahuja C, Goyadi PK: Down Syndrome with Moyamoya Disease: A case series. J Pediatr Neurosci. 2018;13:201–4.

e23. Cho JH, Choi E-K, Moon IK, et al.: Chromosomal abnormalities and atrial fibrillation and ischemic stroke incidence: a nationwide population-based study. Sci Rep 2020; 10: 15872.

e24. Sobey CG, Judkins C, Sundararajan, Phan TG, Drummond GR, Srikanth VK: Risk of major cardiovascular events in people with Down Syndrome. PLoS One 2015; 10: e0137093.

e25. Melville CA, Cooper SA, McGrother CW, Thorp CF, Collacott R: Obesity in adults with Down syndrome: a case-control study. J Intellect Disabil Res 2005; 49: 125–33.

e26. Hasle H, Clemmensen IH, Mikkelsen M: Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000; 355: 165–9.

e27. Cutler AT, Benezra-Obleiter R, Brink SJ: Thyroid function in young children with Down syndrome. Am J Dis Child. 1986; 140: 479–83.

eTABLE 1

Alzheimer's dementia in Down syndrome (DS-AD) and late-onset myoclonic epilepsy in Down syndrome (LOMEDS)

Etiology / connection with Trisomy 21	Clinical syndrome	Diagnostic evaluation	Symptomatic treatment
Alzheimer's dementia in Down syndrome (DS-AD)			
The gene encoding the amyloid precursorprotein is located on chromosome 21. → Often but not always triplicated in people with DS. Leads to increased formation of β-amyloid aggregates with distribution pattern typical of AD pathology.	Dementia and at least one of the following core characteristics: – memory deficit – behavioral change – loss of abilities (independence)	• neuropsychology: e.g., CAMDEX-DS, DTIM (14) • MRI: loss of volume (temporal, frontal, hippocampus, cerebellum) (14) • CSF evaluation, in future probably also blood-based biomarkers (14) • PET imaging (FDG-PET, amyloid-PET, tau-PET) (14)	• cholinesterase inhibitors (14): donepezil 5–10 mg/d, EL: 1 RG: 0; rivastigmine: 6–12 mg/d EL: 4 RG: 0, RG 0; galantamine: 24–32 mg/d EL: 4, RG: 0. • supportive therapy (14): eg., cognitive stimulation programs or self-maintenance therapy (SMT)
Late-onset myoclonic epilepsy in Down syndrome (LOMEDS)			
Arising from the 4th and 5th decades onward. Associated with the appearance of AD pathology.	generalized tonic-clonic seizures (e2) – myoclonus without impaired concentration (usually of the upper limbs, but also of the head and trunk, often upon awakening) – in further course: non-epileptic myoclonus	• EEG (e3): – initial stage: Slowing, mainly frontal SW and ShW – in further course: progressive slowing, generalized pSW, SW	• anticonvulsant drugs (18) drugs of first choice: – levetiracetam: 500–1 500 mg, EL: 4 RG: B alternatives: – valproate up to max.15 mg/kg BW, EL: 4 RG: B – brivaracetam 50–150 mg EL: 4 RG: B – perampanel 2–8 mg, EL: 4 RG: B

AD, Alzheimer's dementia; BW, body weight; CAMDEX-DS: The Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; DS, Down syndrome; EEG, electroencephalography; EL, evidence level; FDG, fluorodeoxyglukose; MRI, magnetic resonance imaging; PET, positron enemission tomography; RG, recommendation grade; SW, Spike waves; ShW, Sharp waves; pSW: Polyspike waves.
Evidence level 1 = randoized, controlled trial(s); 2 = case-control study(studies); 3 = non-analytic case study (studies); 4 = expert opinion
Recommendation grade A = strong recommendation (must); B = recommendation (should); 0 = open recommendation (may)

eTABLE 2

Common mental illnesses in persons with Down syndrome (DS)*

Etiology / connection with Trisomy 21	Clinical syndrome	Diagnostic evaluation	Symptomatic treatment
Affecgtive disorders (unipolar depression)			
No clear link to Chromosome 21 Major role of environmental factors (e.g. stress; changes of daily routine)	loss of interests, lack of drive, joylessness, reduced resilience and everyday competence, sleep disturbances, social withdrawal	main and secondary manifestations according to ICD-10: the more common manifestations in DS are social withdrawal, impaired daily living skills, sleep disturbances, reduced affective modulability	• SSRI (e4, e5) (e.g., sertraline 75–150 mg; EL: 4 RG: A). • mirtazapine (e5) (7.5–45 mg; EL: 4 RG: A) well tolerated by the heart, but weight gain • tricyclic agents (e5, 21) not recommended because of their anticholinergic effects (EL: 4 RG: A)
Psychotic disorders			
No clear link to chromosome 21 (more common than in the general population, but probably less common in DS than in other developmental disorders)	content resembling early-onset psychotic disorder (early-onset schizophrenia) with simple hallucinations, childlike fantasies, mistrust with social withdrawal	main and secondary symptoms according to ICD-10, as in early-onset schizophrenia (EOS), are often not determinative; must be differentiated from anxiety	• antipsychotic drugs (e5-e7) (e.g., risperidone 0.5–5 mg, aripiprazole 7.5–15 mg; both EL: 4 RG: B). • no primary use of substances likely to cause weight gain (e.g., olanzapine, quetiapine) or motor side effects (e.g., haloperidol); both EL: 4 RG: A.
Obsessive-compulsive disorder (OCD)			
Common, but no clear link to chromosome 21 is known	recurring ideas and impulses that disturb patients stereotypically over and over again	main and secondary symptoms according to ICD-10; the main differential diagnosis between compulsive and stereotypic behaviors is challenging in DS	• SSRI (e4, e7) (e.g., sertraline 100–200 mg; EL: 4 RG: B) or antipsychotic drugs (e.g., risperidone 0.5–5 mg, aripiprazole. 7.5–15 mg; both EL: 4 RG: B). SSRI should be tried first because of their more favorable side-effect profile
Autism spectrum disorders (ASD)			
Evidence for association of autism spectrum disorder (ASD) development with DYRK1A – variable reported prevalence figures	DS and ASD associated with lower cognitive performance, more common language impairment, diminished adaptability, and more stereotypic behaviors	main and secondary symptoms according to ICD-10; disturbances of social interaction and communication,as well as stereotypic and repetitive behaviors there may be stereotypical self-injury and irritability	• risperidone (e8) in a low dose (0.5–2 mg/d; EL: 4 RG: B) for, e.g., stereotypic behaviors or tantrums • aripiprazole (e8) (7.5–20 mg/d; EL: 4 RG: 0), haloperidol (0.5–2.5 mg/day; EL: 4 RG: B) where appropriate. • SSRI (e4, e8) (e.g., sertraline 75–150 mg; EL: 4 RG: A or fluoxetine (10–40 mg/day; EL: 4 RG: B – beware of high potential for interactions)

*In all disorders, somatic causes of behavioral changes must be ruled out (see text). Multimodal treatment should be offered that includes pharmacotherapy, psychotherapeutic interventions, and psychosocial interventions adapted to the abilities and skills of the affected individuals. Specific to obsessive-compulsive disorder: multimodal cognitive behavioral therapy with exposure exercises, as well as habit reversal techniques. The available diagnostic scales for the individual disorders (e.g., the Hamilton Depression Scale for depression and the Autism Diagnostic Observation Schedule (ADOS) for ASD) have not been validated for people with DS; if these are used uncritically, there is a risk of false-positive findings. Nor have any specific randomized and controlled trials been performed; for ASD, the recommendations are based on the AWMF-S3 guideline (e8), which, however, did not involve any explicit study of ASD as a comorbidity of DS.

Evidence level 1 = randoized, controlled trial(s); 2 = case-control study(studies); 3 = non-analytic case study (studies); 4 = expert opinion
Recommendation grade A = strong recommendation (must); B = recommendation (should); 0 = open recommendation (may)
EL, evidence level; RG, recommendation grade