Down Syndrome in a Population of Elderly Mentally Retarded Patients: Genetic-Diagnostic Survey and Implications for Medical Care

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Ninety-six adults with Down syndrome (DS) from an institutional setting of 591 mentally retarded were investigated systematically with respect to cytogenetic diagnosis, mental functioning and dementia, ophthalmological and audiological abnormalities, and thyroid function. Seventy of the 96 DS patients (73%) were older than 40 years. Only 4.2% were females. Trisomy 21 was found in 86% and mosaic trisomy 21 in 13%. Eighty-two percent of the patients were moderately or severely mentally retarded, 15% were profoundly retarded, and only 3% mildly retarded. Nineteen percent of the patients had dementia. This number increased to 42% of the patients above the age of 50 years. Epileptic seizures were present in 16.7% of all patients, and in 50% of the patients with dementia. Only 17% of the patients in the present study had normal visual acuity, one-third had at least moderately reduced vision. This number increased significantly with age: in the age group 50–59 years almost half of the patients had moderate to severe vision loss. Seventy percent of the patients had moderate, severe, or very severe hearing loss, which was undiagnosed before systematic hearing testing was performed. Increased (48%) or decreased (1%) TSH level was found in 49% of the patients examined for thyroid functions. We suggest a regular screening of all adults with DS to diagnose early dementia, epilepsy, hypothyroidism, and early loss of visual acuity and hearing, with special attention to the group of patients who are severely to profoundly mentally retarded and those with advanced age. Cytogenetic studies are necessary to con-firm the clinical diagnosis and are essential for genetic counseling purposes. Am. J. Med. Genet. 85:376–384, 1999. © 1999 Wiley-Liss, Inc.

INTRODUCTION

Down syndrome (DS) is the most frequently identified cause of mental retardation, with an incidence of 1/700 to 1/1,000 births [Evers-Kiebooms et al., 1982; Harper, 1994]. The phenotype is well delineated and results from the presence of a trisomy of the chromosomal 21q22.1-q22.3 region [Mattei et al., 1981; Korenberg et al., 1990; Jones, 1997]. The DSCR1-gene (Down Syndrome Critical Region 1) in the 21q22.1-q22.2 region is reported as a candidate gene in the pathogenesis of DS, particularly in mental retardation and heart defects, and is highly expressed in brain and heart [Fuentes et al., 1995]. Approximately 94% of DS present a classical trisomy 21, while in 2.4% mosaicism is found. In about 3.3% a de novo or familial translocation is the cause of trisomy 21 [Evers-Kiebooms et al., 1982].

Life expectancy in DS is reduced [Thase, 1982]: the major cause for early mortality is congenital heart defects [Jones, 1997]. Although the average life expectancy in DS has increased over the last years, it still remains lower compared to the general population [Thase, 1982; Dupont et al., 1986; Buchanan, 1990; McGrother and Marshall, 1990]. Susceptibility to infections is a well-known feature and is related to an abnormal serum IgG subclass pattern [Annerén et al., 1992]. The incidence of leukemia, various thyroid disorders, such as athyreosis, subclinical hypothyroidism, and hyperthyroidism, and auto-immune disorders are increased [Buchanan, 1990; Norman et al., 1995]. With advancing age, premature aging is observed, accompanied by several complications: premature graying or loss of hair, hearing problems and presbyacusis, loss of

visual acuity and cataracts, and Alzheimer dementia in early adulthood.

In the present study, we systematically investigated 96 patients with DS derived from a population of 591 institutionalized mentally retarded patients. This study was set up to inventory important clinical complications in a group of adult patients with DS.

MATERIALS AND METHODS
Patients

During a systematic etiological survey over the period 1991–1995 in the Institute of Mentally Retarded Patients "Huize Assisië," Udenhout, The Netherlands, 96 patients (92 males (95.8%) and 4 females (4.2%)) with clinical features of DS were selected out of a population of 591 patients. Historically, only male patients were living in the institute and presently only 6.6% of the residents are female. Patient records were studied and a physical examination was performed. Written permission to perform cytogenetic studies was obtained from the legal representative of patients who had not been karyotyped before.

Cytogenetic Studies

GTG-banded chromosomes from cultured peripheral lymphocytes were studied in 87 of the 96 patients (90.6%). In one patient, cultured fibroblasts were also karyotyped. In nine individuals (9.4%), chromosomal investigation was refused. However, these patients were included in the present study on the basis of their clinical diagnosis.

Mental Functioning

All patients were tested by the educational psychologists of the institute to determine their level of intellectual functioning. Several psychological tests, adapted for the Dutch population, were used, depending on the level of mental functioning. In patients with a developmental level between 7 and 11 years [mildly mentally retarded (IQ level 50–55 to 70)], the Wechsler Intelligence Scale for Children-Revised (WISC-R) [Van Haasen et al., 1986] was used. The Wechsler Primary Preschool Scale of Intelligence test (WIPPSI) [Stinissen and Vander Steene, 1970] was used in the group of patients with a developmental level between 4 and 7 years (moderately mentally retarded (IQ level 35–40 to 50–55)). Three different tests were applied in the group of patients who were severely (developmental level between 18 months and 4 years (IQ level 20–25 to 35–40)) or profoundly mentally retarded (developmental level between 12 months and 18 months (IQ level below 20–25)). The first test was the KID-N (Kent Infant Development Scale) [Schneider et al., 1990], a developmental scale between 1 and 14 months consisting of five subscales including cognition, motor development, language, personal autonomy, and social skills. The second test was the Bayley Developmental Scales (BOS 2-30) [Van der Meulen and Smrkovsky, 1983] and included a mental scale and motor scale. The third test was the Terman-Merrill intelligence scale [Stinissen, 1965] constructed to test cognition levels corresponding to the ages of 2 years and 22 years. The mental level of the patients was classified according to the criteria described in the Diagnostic and Statistic Manual of Mental Disorders, 4th edition (DSM IV) [APA, 1994]. Both the intellectual impairment and the adaptive behavior of the individual was used to classify patients.

Dementia

Medical and psychiatric causes leading to a dementia-like picture were excluded by the general practitioner of the institute. Memory and orientation skills were examined by several questionnaires adapted for the Dutch population which were filled out by day care workers. The scales included the DMR (the Dementia Questionnaire for Mentally Retarded Persons) [Evenhuis et al., 1992], the Observatielijst Ouderwordende Bewoners (Observation List for Aging Residents) [Hoefnagel, 1989], and the Sociale Redzaamheidsschaal (SRZ) (Daily Living Skills) [Kraijer and Kema, 1990]. Dementia associated with DS was considered as not attributable to a specific medical or psychiatric diagnosis.

Ophthalmologic Examination

In 92 of the 96 patients, visual acuity could be tested by different tests depending on the intellectual level of the patients. In the group of patients who are mildly or moderately mentally retarded the Landolt ring chart was used and in the group of severely mentally retarded patients the Burghardt picture charts for distant vision. The group of profoundly mentally retarded could not be tested by any objective test. In these patients, visual acuity was estimated by observation and registration of the eye movements and eye contact. Some patients were referred for specialist diagnosis and treatment. A Chi-square test was used to determine whether there was a correlation between the level of mental retardation and loss of visual acuity.

Hearing Examination

Different audiometric methods were used depending on the level of mental retardation, cooperation, and concentration possibilities of the individual patient. Although some patients had hearing aids, each patient was tested without correction. In the group of mildly and moderately mentally retarded patients, hearing on each side was tested using pure tone (play audiometry) and speech audiometry (speech audiometry with pictures) (Interacoustics AC 40, serial number 0004 1.13). The mean hearing loss was calculated according to the Fletcher-high index (mean loss at 1,000, 2,000 and 4,000 Hz). Hearing impairment in patients with severe and profound mental retardation was tested by free field audiometry (behavior observation audiometry). In this setting, hearing loss of the best ear was diagnosed, and mean hearing loss was calculated according to the Fletcher-high index. The classification system included mild (16–30 dB), moderate (31–60 dB), severe (61–90 dB), and profound (>90 dB) hearing loss. Although there is a mild hearing loss from 16 dB on, we considered hearing loss clinically important when there was a mean hearing loss of ≥30 dB in the best ear. The mo-

TABLE I. Classification of the Population Down Syndrome Patients According to Age and Mental Level

IQ Level	≤29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	≥60 yrs	Total
Mild (50–55 to 70)	1 (11.1%)	1 (5.9%)	—	—	1 (100%)	3 (3.1%)
Moderate (35–40 to 50–55)	5 (55.6%)	10 (58.8%)	12 (33.3%)	19 (57.6%)	—	46 (47.9%)
Severe (20–25 to 35–40)	3 (33.3%)	5 (29.4%)	18 (50%)	7 (21.2%)	—	33 (34.4%)
Profound (<20–25)	—	1 (5.9%)	6 (16.7%)	7 (21.2%)	—	14 (14.6%)
Total	9 (100%)	17 (100%)	36 (100%)	33 (100%)	1 (100%)	96 (100%)

bility of the tympanum was also tested by impedance tympanometry (Grason Stadler, GSI 33). The middle ear reflex could not be tested since there was a problem of interpreting the ipsilateral or contralateral reflexes. According to Katz [1994], the following criteria were used: the ear canal volume (ECV) for adults is normal, within the range 0.65–1.75 cm^2, the middle ear pressure (MEP), at or near normal atmospheric pressure, is normal within the range of 0 to −100 daPa, and the static compliance (SC), which is determined by the impedance of tympanum and middle ear bones at 226Hz, is normal within the range of 0.30–1.60 cm^2.

Thyroid Function

In 90 patients, serum TSH levels [Delfia hTSH assay (Pharmacia, Woerden, The Netherlands)] and serum T4 levels (Double Antibody Total T4 assay (Diagnostic Products Corporation)) were tested.

RESULTS
Patients

The mean age of the 96 DS patients was 44.8 years, ranging from 22–61 years. More than 70% of the patients were between the age of 40–49 and 50–59 years (Table I). During the study period, 10 patients died and 7 were diagnosed with epilepsy.

Cytogenetic Studies

Eighty-seven patients were karyotyped. In 75 patients (86.2%) full trisomy 21 (2 females and 73 males) was diagnosed and in 11 patients (12.6%) trisomy 21 mosaicism (Table II). In patient 10 an autosomal reciprocal translocation t(11;17)(q13;q25) was found in the two euploid cells: 47,XY,+21/46,XY,t(11;17)(q13;q25) de novo. Patient 11 showed a mosaic pattern of double aneuploidy: 45X/46,X,+21/47,XY,+21 (79/2/19) in peripheral lymphocytes and a different mosaicism 45,X/47,XY,+21 (36/14) in cultured fibroblasts. In one patient (1.1%) a de novo (21;21) translocation was present.

Mental Function

Table I shows the mental level according to age. Seventy-three percent of the patients with DS were older than 40 years. More than 82% of the patients were moderately or severely mentally retarded. However, in the age group of 40–49 years, 66% of the patients were severely or profoundly and 33% moderately mentally retarded (Table I).

Of the 11 patients with trisomy 21 mosaicism, one was mildly mentally retarded, four moderately, five severely, and one profoundly (Table III). The one mildly

mentally retarded patient with trisomy 21 mosaicism was a 61-year-old male who was able to write and read and has a mosaic pattern of double aneuploidy (Down-Turner patient) (Table II).

Dementia

In 18 of the 96 patients (18.8%), a diagnosis of dementia was made. The incidence of dementia increased significantly with age, with 4 (11.1%) patients in the 40–49 year group and 14 (42.4%) patients in the 50–59 year group. Most patients with dementia were also moderately mentally retarded (Table IV). In this last group, 6 of the 14 patients with dementia died during the period of this study and also suffered from epilepsy. Epileptic seizures were present in 16 of the 96 DS patients; nine of these patients subsequently developed dementia.

Ophthalmologic Examination

In 16 of the 92 examined patients vision was normal (17.4%). However, in five (one patient with moderate, two with severe, and two with profound mental retardation) vision could not be extensively tested due to lack of cooperation. As shown in Table V, more than 50% of the patients had a mild vision loss, which could be corrected in almost half of them. Moderate loss of visual acuity was diagnosed in 19 patients (20.7%). A severe to very severe vision loss was detected in eight patients (8.7%) and correction was not possible. Table VI shows the different age categories in association with loss of visual acuity. At a younger age, loss of visual acuity was rather mild, but with advancing age the severity of vision loss increased: in the age group 50–59 years almost half of the patients (13 out of 29, 44.8%) had moderate to severe vision loss, compared to 27.8% in the age group 40–49 years and 17.7% in the age group 30–39 years. Table VII presents an overview of the level of mental functioning and severity of vision

TABLE II. Patients With Mosaicism and Cell Line Distribution

Patient	Sex	46,XY or XX Number of cells	47,XY,+21 or XX,+21 Number of cells
1	M	6	44
2	M	3	27
3	M	9	6
4	M	2	48
5	M	13	19
6	M	7	23
7	M	13	37
8	F	37	13
9	F	4	29
10	M	46,XY,t(11;17)/47,XY,+21(2/30) de novo	
11	M	45,X/46,X,+21/47,XY,+21 (79/2/19)	

TABLE III. Relation Level of Mental Retardation and Karyotype

Karyotype	Unknown	Full T21	Mosaic	Translocation	Total
Mental retardation					
Mild	—	2 (2.7%)	1 (9.1%)	—	3 (3.1%)
Moderate	6 (66.7%)	35 (46.7%)	4 (36.4%)	1 (100%)	46 (47.9%)
Severe	1 (11.1%)	27 (36%)	5 (45.5%)	—	33 (34.4%)
Profound	2 (22.2%)	11 (14.7%)	1 (9.1%)	—	14 (14.6%)
Total	9 (100%)	75 (100%)	11 (100%)	1 (100%)	96 (100%)

loss. No statistically significant correlation was found between the severity of mental retardation and loss of visual acuity (Chi-square in contingency table (2 × 3); $P = 0.08$; 2 degrees of freedom).

In 65 patients, a more specific ophthalmologic diagnosis was made. In 28 (43%), two or more different eye abnormalities were present. In 26 patients cataracts were present, bilateral in 23. Of the seven patients with a severe form of cataracts, five received extraction of the lens (with lens reimplantation in two). Keratoconus was diagnosed in 11 patients, bilateral in eight. Refraction problems included myopia (n = 16), hypermetropia (n = 6), and astigmatism (n = 9). Strabismus was noted in 21 patients: convergent in 12, alternans in four, divergent in one, and amblyopia in four. In ten patients other eye problems were diagnosed: nystagmus (n = 3), pterygium (n = 2), macular degeneration (n = 1), atrophia of the iris (n = 1), phtisis bulbi (n = 1), ablatio retinae (n = 1), and cone and rod cell dysfunction (n = 1).

Hearing Problems

Information on hearing could be obtained from 90 of the 96 patients. Data were already available on ten patients and included three with normal hearing, six with mild hearing loss, and one with moderate hearing loss. None of these ten patients had hearing aids.

Table VIII presents hearing loss in relation to age of all 90 patients. Sixty-five patients (72.2%) had moderate, severe, or profound hearing loss. Bilateral hearing devices were used in 31 patients. Patients with a unilateral prosthesis had moderate hearing loss (Table IX).

Table X presents an overview of the type of hearing loss of the best ear diagnosed in these 80 patients. Of one patient no information about the type of hearing loss could be obtained. Mixed hearing loss was diagnosed in 45%, perceptive hearing loss in 43.8%, and conductive hearing loss in only 10% of the patients.

Tympanometry was also performed in these 80 patients. In 45 (56.3%) patients, abnormalities of the mobility of the tympanum was noted: in 29 patients bilateral, in ten on the right side, and in six patients on the left side. Data on reflexes of the bones could not be obtained.

Thyroid Function

Data on serum T4 and TSH levels for 90 patients were available. The T4 level was normal in 87 patients (96.7%) and in three patients (3.3%) the T4 concentration was below 0.07 μmol/l and hypothyroidism was diagnosed. Thirteen patients were treated by exogenous T4 including the three patients with hypothyroidism. Table XI presents the distribution of the TSH levels in relation to age: no significant correlation between increased TSH levels and the different age groups was found (Chi-square in contingency table (2 × 3); $P = 0.17$; 2 degrees of freedom).

DISCUSSION

In this systematic etiological study in an institutionalized population of adult mentally retarded individuals, we collected data on the physical and cognitive functioning of the 96 trisomy 21 patients (16.2% of the total population). More than 70% of the patients were above 40 years (mean age 44.8 years). Until recently, only male residents had been admitted to the institute, explaining why only four females participated in this study. All patients were first selected according to their clinical phenotype. Chromosome studies could be performed in 87 of the 96 patients, and the clinical diagnosis of trisomy 21 was confirmed in all these patients. A full trisomy 21 was found in 86.2% of the patients, in contrast to the general findings in the literature (94%) [Evers-Kiebooms et al., 1982]. In the present study, 12.6% of the patients had mosaic trisomy 21, which is higher than the 2.4% found in the overall Down syndrome population studies. This higher percentage of mosaic trisomy 21 in this older population may be due to the fact that patients with milder clinical phenotype, as seen in trisomy 21 mosaicism, reach an older age. In one mosaic patient, an apparently balanced autosomal reciprocal translocation t(11;17)(q13;q25) was present

TABLE IV. Classification of Down Syndrome Patients With Dementia According to Age and Mental Level

IQ Level	40–49 yrs	50–59 yrs	Total
Mild (50–55 to 70)	—	—	—
Moderate (35–40 to 50–55)	1	9	10
Severe (20–25 to 35–40)	3	2	5
Profound (<20–25)	—	3	3
Total	4	14	18

TABLE V. Results of Vision Tested in 92 Patients*

Vision	+C	−C	Total
Normal	—	16	16
>0.30 (mild)	24	25	49
≤0.30	13	6	19
0.02–0.05 (severe)	—	2	2
<0.02 (severe/blind)	—	6	6
Total	37	55	92

*+C: with correction; −C: without correction.

TABLE VI. Classification of the Population of Down Syndrome Patients According to Age and Loss of Visual Acuity

	≤29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	≥60 yrs	Total
Normal	2 (22.2%)	2 (11.8%)	8 (22.2%)	4 (13.8%)	—	16 (17.4%)
>0.30	6 (66.7%)	12 (70.6%)	18 (50%)	12 (41.3%)	1 (100%)	49 (53.3%)
0.05–0.30	1 (11.1%)	2 (11.8%)	6 (16.6%)	10 (34.5%)	—	19 (20.7%)
0.02–0.05	—	—	1 (2.8%)	1 (3.4%)	—	2 (2.2%)
<0.02	—	1 (5.9%)	3 (8.3%)	2 (6.9%)	—	6 (6.5%)
Total	9 (100%)	17 (100%)	36 (100%)	29 (100%)	1 (100%)	92 (100%)

in the cell line with 46 chromosomes. Normal/autosomal reciprocal translocation mosaicism is rare [Fryns and Kleczkowska, 1986; Kleczkowska et al., 1990]. As far as we know, no other patient with trisomy 21 mosaicism and a de novo autosomal reciprocal translocation in the normal cell line has been reported so far. In one other mosaic patient, chromosomal analysis showed a mosaic pattern of double aneuploidy: 45X/46,X,+21/47,XY,+21 (79/2/19) in cultured peripheral lymphocytes and a different mosaic pattern 45,X/47,XY,+21 (36/14) in cultured fibroblasts. This patient has previously been reported [Van Buggenhout et al., 1994]. He presented a mixed phenotype with DS features (mild mental retardation, brachycephaly, upward slanting palpebral fissures, flat midface, and short stature) as well as features of Ullrich-Turner syndrome (short and broad neck, low posterior hairline, wide thorax, large internipple distance, and short stature).

Mental Function

More than 80% of the patients were moderately or severely mentally retarded. In the 50–59 year age group, 60% of the patients were moderately and 40% severely to profoundly mentally retarded, whereas at 40–49 years, 66% of the patients were severely and only one-third moderately mentally retarded.

Some studies indicated that patients with trisomy 21 mosaicism have better cognitive function [Fishler and Koch, 1991]. In the present study, this observation could not be confirmed since 4/11 patients were moderately and 5/11 patients severely mentally retarded.

Dementia

Previous studies [Warren et al., 1989; Evenhuis et al., 1991; Pueschel et al., 1995] have extensively documented the high prevalence of dementia and Alzheimer's disease in DS, which affects more than 25% of individuals above the age of 50 years. The neuropathological findings [Norman et al., 1995] of senile plaques and deposition of amyloid protein in DS patients 20–30 years earlier than in a population without DS may be related to the increased dosage of a gene for the amyloid precursor protein on the proximal 21q region [Norman et al., 1995]. The overall percentage of trisomy 21 patients with dementia in the present study is high (18.75%) and significantly increases with age. No symptoms of dementia were noted in the 24 patients younger than 39 years, but symptoms were noted in 11.1% of the patients in the age group 40–49 years and in 42.4% of the patients in the age group 50–59 years. This high percentage of dementia cannot be explained by selective admission of DS patients with dementia. In this institute, all residents have been admitted as young adolescents for lifelong care. There was no correlation between the dementia and the level of mental retardation (Chi-square in contingency table (2 × 3); $P = 0.8$; 2 degrees of freedom).

During this study, ten patients died, seven had dementia, and six were in the age group 50–59 years. This observation confirms that dementia is an important predictive factor for (limited) life prognosis in the group of adult DS patients, especially after the age of 50 years. However, dementia was not correlated with the level of mental retardation.

In DS patients, a high prevalence of seizures has been noted in the third decade of life [Pueschel et al., 1995] and at an older age, seizure disorders were usually associated with Alzheimer's disease [Pueschel et al., 1995]. In the study of Evenhuis [1990], the incidence of epileptic seizures and myoclonus increased about 8-fold in demented patients with DS as compared to patients with Alzheimer dementia but without DS. In the present study, 9 of the 18 patients (50%) with dementia also suffered from epileptic seizures. Epileptic seizures were considered one of the first signs of Alzheimer dementia by the general practitioners in this institute.

Ophthalmologic Problems

Only 16 of the 92 patients (17.4%) had normal visual acuity. More than 50% had a mild vision loss, 20.7% had moderate loss of visual acuity, and severe to very

TABLE VII. Relation Level of Mental Retardation and Loss of Visual Acuity

	Mental retardation				
	Mild	Moderate	Severe	Profound	Total
Normal	1 (33.3%)	4 (9.1%)	7 (22.6%)	4 (28.6%)	16 (17.4%)
>0.30	2 (66.6%)	23 (52.3%)	19 (61.3%)	5 (35.7%)	49 (53.3%)
≤0.30	—	14 (31.8%)	3 (9.7%)	2 (14.3%)	19 (20.7%)
0.02–0.05	—	1 (2.3%)	1 (3.2%)	—	2 (2.1%)
<0.02	—	2 (4.5%)	1 (3.2%)	3 (21.4%)	6 (6.5%)
Total	3 (100%)	44 (100%)	31 (100%)	14 (100%)	92 (100%)

TABLE VIII. Classification of the Population of Down Syndrome Patients According to Age and Hearing Loss

	≤29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	≥60 yrs	Total
0–15 dB	1 (11.1%)	—	4 (11.4%)	1 (3.4%)	—	6 (6.7%)
16–30 dB	4 (44.4%)	9 (56.3%)	3 (8.6%)	3 (10.3%)	—	19 (21.1%)
31–60 dB	3 (33.3%)	5 (31.3%)	20 (57.1%)	20 (69%)	—	48 (53.3%)
61–90 dB	1 (11.1%)	2 (12.5%)	6 (17.1%)	5 (17.2%)	1 (100%)	15 (16.7%)
>90 dB	—	—	2 (5.7%)	—	—	2 (2.2%)
Total	9 (100%)	16 (100%)	35 (100%)	29 (100%)	1 (100%)	90 (100%)

severe vision loss was diagnosed in 8.7%. With advancing age (50–59 years age group), 44.8% of the patients had moderate to severe vision loss, compared to 27.8% in the age group 40–49 years and 17.7% in the age group 30–39 years. No correlation was found between the severity of the vision loss and the degree of mental handicap.

Cataracts (28.3%), strabismus (22.8%), refraction problems (33.7%), and keratoconus (12%) were the main ophthalmological problems.

Warburg [1982] performed a large study in Denmark and concluded that 5% of the mentally retarded children had a visual acuity below 0.1, as compared to 0.02% in the normal child population.

In the older (50–65 years) population of persons with intellectual disability, prevalence of visual impairment ranges from 8–50% [Janicki and Jacobson, 1986; Moss, 1991]. However, none of these authors reported any diagnostic criteria.

In a population of approximately 3,000 mentally handicapped individuals, Moss [1991] observed that severe visual problems tended to be higher in the early and late years compared to mid-life. Also, Evenhuis [1995a] suggested a higher prevalence of visual impairment in the elderly population with mental retardation as compared to the general aging population.

Several studies were published on eye defects in developmentally handicapped children and a high percentage of abnormalities was present. A relationship between visual problems and developmental handicap was thus considered [Edwards et al., 1972; Kennerley Bankes, 1974]. Also, Warburg [1982] observed that more severe visual impairment is seen in more severe intellectual disability.

Several authors reported on the ocular findings in DS [Eissler and Longenecker, 1962; Cullen and Butler, 1963; Gardiner, 1967; Walsh, 1981; Shapiro and France, 1985; Caputo et al., 1989]. Cullen and Butler [1963] reported on a population of 143 patients with DS between the ages of 2–53 years and observed ocular

defects in 65.5%. In a study by Gardiner [1967], 70% of the 22 patients with DS had defective visual acuity in comparison to 30% of the 38 patients with another mental handicap. Aitchison et al. [1990] reported on a large group of 367 patients with mental retardation, with 144 patients older than 40 years and 105 males and 262 females, including 31 patients with DS. In 218 patients (59%), eye abnormalities were found; excluding the patients with DS, this percentage was still high (54%). The most common eye problems included strabismus (31%), refractive error (30%), and cataract (11%) in this total population. In this group of patients with DS, 71% were older than 40 years.

Jacobson [1988] reported on a group of 228 mentally retarded patients. DS was present in 50 patients and in 22 of these patients visual acuity was below 0.1. In 14 of these 22 patients, an acquired visual handicap was present and included presenile cataract, high myopia, and keratoconus.

Almost one-third of the patients in our study had a moderate to severe vision loss, resulting in a serious limitation in functioning. In 53.3% of the patients a mild loss of visual acuity was diagnosed and 50% received correction. This group of patients with a mild loss of visual acuity should be carefully treated and regularly screened from the age of 35–40 years, since our data suggest that with advancing age more patients are found with severe loss of visual acuity. However, to confirm this observation follow-up studies are necessary. In keeping with the committee report recommendations [Pueschel et al., 1995], we support repeated eye examination at least every 2 years in adult patients with DS to diagnose early loss of visual acuity and other eye problems at increasing frequency with advancing age. Therefore, the general practitioner should not wait for spontaneous complaints or observations of the care givers. A study by Kelly [1996] showed that it is possible for nurses to carry out a basic examination, including external inspection, lid eversion, and pupil testing and to perform simple eye testing effectively (distance and near vision and peripheral vision testing).

Hearing Loss

Only 6.7% of the 90 participating patients in the present study had normal hearing. A mild hearing loss of the best ear was present in 21.1%. More than 70% of the patients had a moderate (53.3%), severe (16.7%), or profound (2.2%) hearing loss. In 41.1%, hearing devices were used, and in 83.8% this was bilateral.

In 80 patients, a more extensive examination to de-

TABLE IX. Distribution of the Patients Who Received Hearing Aids (HA)

Degree of hearing loss	Without HA	With HA	Total
Normal	6	—	6
Mild	19	—	19
Moderate	20	28	48
Severe	7	8	15
Profound	1	1	2
Total	53	37	90

TABLE X. Severity of Hearing Loss in Relation to the Type of Hearing Loss and According to Age (in Years)

| | <29 yrs | | | 30–39 yrs | | | 40–49 yrs | | | 50–59 yrs | | | >60 yrs | |
	M	P	C	M	P	C	M	P	C	M	P	C	M	Total
Normal	1	—	—	—	—	—	—	—	1	—	1	—	—	3
Mild	2	2	—	—	6	2	—	1	—	—	—	—	—	13
Moderate*	3	—	—	2	3	—	8	7	3	9	10	1	—	46
Severe	1	—	—	1	1	—	3	1	2	3	2	—	1	15
Profound	—	—	—	—	—	—	2	—	—	—	—	—	—	2
Total	7	2	—	3	10	2	13	9	6	12	13	1	1	79

M, mixed hearing loss; P, perceptive hearing loss; C, conductive hearing loss.
*No specific information available on one patient of 43 years with a moderate hearing loss.

termine the type of hearing loss was performed: an equal number of patients had mixed or perceptive and 10% had conductive hearing loss. Conductive hearing loss was present in the age groups from 30–59 years. With advancing age, more patients with a moderate, severe, or profound hearing loss were noted.

The prevalences of severe congenital perceptive hearing loss is estimated at 1/1,000 newborns. Reviewing the literature, Trommelen and De Bal [1994] found the prevalence of hearing loss in persons with mental retardation to vary from 7–52%, and Mul et al. [1997] noted prevalence between 40–90% in persons with DS. Evenhuis [1996] reported hearing problems in 40% of DS children and noted that perceptive hearing loss increases from age 20 on. Buchanan [1990] estimates the onset of presbyacusis in patients with DS to occur 20 to 30 years earlier than in patients with other causes of mental retardation and 30 to 40 years earlier than in the normal population. Hearing loss is reported in 70% of the patients with DS above the age of 40 years [Evenhuis, 1991, 1992, 1995b].

Impacted cerumen in the narrow ear canals and chronic otitis media, due to Eustachian tube dysfunction, results in conductive hearing loss, and are the main causes for hearing loss in children and young adults with DS [Dahle and McCollister, 1986; Brown et al., 1989; Evenhuis, 1991; Crandell and Roeser, 1993; Maurizi et al., 1995]. Crandell and Roeser [1993] observed impacted cerumen was present in 28% of patients with mental retardation compared to 2–6% in the general adult population. In patients with DS older than 40 years, hearing loss is caused by continuous effusion of chronic otitis media and presbyacusis resulting in perceptive hearing loss [Evenhuis, 1991; Buchanan, 1990]. This may explain the distribution of perceptive (43.8%) and mixed type of hearing loss (45%) in the present group of older patients.

Mul et al. [1997] observed that 85% of the patients without hearing aids did not know that they suffered from hearing loss and for 80% of the patients, the general practitioner or their care givers did not know about hearing loss.

Hearing impairment in patients who were severely or profoundly mentally retarded could be diagnosed by behavior observation audiometry, in which the hearing loss of the best ear was diagnosed. Meanwhile, Verpoorten and Emmen [1995] developed a tactile-auditory conditioning method for difficult-to-test populations. The majority of patients in the present population were also examined for the mobility of the tympanum by impedance audiometry to diagnose middle ear problems. In 56.3% of the 80 patients, abnormalities of the tympanum were noted.

Depression and severe hearing loss are difficult to differentiate from dementia and are often present in patients with DS [Warren et al., 1989; Evenhuis et al., 1991; Norman et al., 1995; Pueschel et al., 1995]. Early diagnosis and treatment can prevent malfunctioning. [Evenhuis, 1991].

Diagnosis of middle ear infections and hearing impairment, and regular cleaning of the external ear canals in children and adults with mental retardation, are important in early intervention [Evenhuis, 1995b].

The present findings reinforce the recommendations of the Committee report [Pueschel et al., 1995] to perform a hearing assessment in adults with DS at least every 2 years.

Thyroid Function

Thyroid dysfunction occurs in about 40% of adults with DS [Pueschel et al., 1995; Dinani and Carpenter, 1990]. Thyroid antibodies are frequently present, suggesting a genetic predisposition to autoimmune thyroiditis. Clinical features of hyperthyroidism include agitation and loss of weight. Features of hypothyroidism are short stature, slow activity, hoarse voice, and obesity [Dinani and Carpenter, 1990].

In the present study, thyroid dysfunction with increased (n = 43) or decreased (n = 1) TSH levels was observed in 44 (48.9%) of the examined patients. Hyperthyroidism was diagnosed in one patient (TSH level decreased) and hypothyroidism in three patients, with only two patients with a primary hypothyroidism (TSH

TABLE XI. TSH-Level in Relation to Age

	<29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	>60 yrs	Total
Normal	4	5	18	18	1	46 (51.1%)
Increased	4	11	17	11	—	43 (47.8%)
Decreased	—	—	1	—	—	1 (1.1%)
Total	8	16	36	29	1	90

increased; T4 decreased) and one patient with a secondary hypothyroidism (TSH normal; T4 decreased). This low percentage can be explained because thyroid screening and treatment were performed on a regular basis before the beginning of the present study. Our percentages are comparable to previous reports [Pueschel and Pezzullo, 1985; Kinnell et al., 1987; Friedman et al., 1989; Dinani and Carpenter, 1990]. In an overview of the literature, Evenhuis [1991] reported a variation of 2.5–17% of hypothyroidism in patients with DS, with a prevalence below 5% under the age of 20 years.

Subclinical hypothyroidism is widely used to describe patients with increased TSH and normal T4, without symptoms of hypothyroidism [Anonymous, 1986]. In the present study, 41 patients were diagnosed with subclinical hypothyroidism and 10 patients were treated. Smink et al. [1992] reported ten patients with DS and observed that TSH was increased in four patients. In a group of 105 children with DS between the ages of 3 months to 20 years, Alembik et al. [1996] demonstrated that one-half of these children had an increased TSH, which improved after thyroxin treatment. The main argument to support treatment of these patients is that it may prevent progression to hypothyroidism and that improved physical and mental well-being is reported [Anonymous, 1986; Cooper et al., 1984]. Therefore, annual screening of T4, TSH, and thyroid antibodies is recommended to identify those who have a thyroid disorder.

CONCLUSION

The findings of the present study confirm the necessity of regular screening in institutionalized older male adults with DS syndrome to diagnose early onset dementia, epilepsy, hypothyroidism, and early loss of visual acuity and hearing. Cytogenetic studies are necessary to confirm the clinical diagnosis. Special attention and care should be given to the subgroups of trisomy 21 patients with severe to profound mental retardation, as these complications lead to serious additional limitations of functioning. Screening programs should be performed with increased frequency (on a yearly basis) with advancing age.

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REFERENCES

Aitchinson C, Easty DL, Jancar J. 1990. Eye abnormalities in the mentally handicapped. J Ment Defic Res 34:41–48.

Alembik Y, Toledo C, Finck S, Stoll C. 1996. Anomalies of thyroid function in Down syndrome children. Eur J Hum Genet 4(Suppl 1):28.

Annerén G, Magnusson CGM, Lilja G, Nordvall SL. 1992. Abnormal serum IgG subclass pattern in children with Down's syndrome. Arch Dis Child 62:628–631.

Anonymous. 1986. Subclinical hypothyroidism (editorial). Lancet 1:251–252.

APA (American Psychiatric Association). 1994. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association.

Brown PM, Lewis GTR, Parker AJ, Maw AR. 1989. The skull-base and nasopharynx in Down's syndrome in relation to hearing impairment. Clin Otolaryngol 14:241–246.

Buchanan LH. 1990. Early onset of presbyacusis in Down syndrome. Scand Audiol 19:103–110.

Caputo AR, Wagner RS, Reynolds DR, Guo S, Goel AK. 1989. Down syndrome: clinical review of ocular features. Clin Pediatr 28:355–358.

Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. 1984. L-thyroxine therapy in subclinical hypothyroidism. Ann Intern Med 101:18–24.

Crandell CC, Roeser RJ. 1993. Incidence of excessive/impacted cerumen in individuals with mental retardation: a longitudinal investigation. Am J Ment Retard 97:568–574.

Cullen JF, Butler HG. 1963. Mongolism (Down's syndrome) and keratoconus. Br J Ophthalmol 47:321–330.

Dahle AJ, McCollister. 1986. Hearing and otologic disorders in children with Down syndrome. Am J Ment Defic 90:636–642.

Dinani S, Carpenter S. 1990. Down's syndrome and thyroid disorder. J Ment Defic Res 34:187–193.

Dupont A, Vaeth M, Videbech P. 1986. Mortality and life expectancy of Down's syndrome in Denmark. J Ment Defic Res 30:111–120.

Edwards WC, Price WD, Weisskopf B. 1972. Ocular findings in developmentally handicapped children. J Pediatr Ophthalmol 9:162–167.

Eissler R, Longenecker LP. 1962. The common eye findings in mongolism. Am J Ophthalmol 54:398–406.

Evenhuis HM. 1990. The natural history of dementia in Down's syndrome. Arch Neurol 47:263–267.

Evenhuis HM. 1991. Veel voorkomende, maar weinig onderkende aandoeningen bij volwassenen met het syndroom van Down. Ned Tijdschr Geneesk 135:1581–1584.

Evenhuis HM. 1992. Evaluation of a screening instrument for dementia in ageing mentally retarded persons. J Intellect Disabil Res 36:337–347.

Evenhuis HM. 1995a. Medical aspects of ageing in a population with intellectual disability. I. Visual impairment. J Intellect Disabil Res 39:19–25.

Evenhuis HM. 1995b. Medical aspects of ageing in a population with intellectual disability. II. Hearing impairment. J Intellect Disabil Res 39:27–33.

Evenhuis HM. 1996. Richtlijnen voor diagnostiek en behandeling van slechthorendheid bij mensen met een verstandelijke handicap. Ned Tijdschr Geneesk 140(37):1851–1854.

Evenhuis HM, Kengen MMF, Eurlings HAL. 1991. Dementie vragenlijst voor zwakzinnigen (DVZ). Lisse: Swets & Zeitlinger.

Evenhuis HM, van Zanten GA, Brocaar MP, Roerdinkholder WHM. 1992. Hearing loss in middle-age persons with Down syndrome. Am J Ment Retard 97:47–56.

Evers-Kiebooms G, Vlietinck R, Fryns JP, Van den Berghe H. 1982. Diverse parameters bij het syndroom van Down (mongolisme) en andere trisomieën in België. CBGS Rapport 50:8.

Fishler K, Koch R. 1991. Mental development in Down syndrome mosaicism. Am J Ment Retard 96:345–351.

Friedman DL, Kastner T, Pond WS, Rice O'Brien D. 1989. Thyroid dysfunction in individuals with Down syndrome. Arch Intern Med 149:1990–1993.

Fryns JP, Kleczkowska A. 1986. Reciprocal translocation mosaicism in man (letter to the editor). Am J Med Genet 25:175–176.

Fuentes J-J, Pritchard MA, Planas AM, Bosch A, Ferrer I, Estivill X. 1995. A new human gene from the Down syndrome critical region encodes a proline-rich protein highly expressed in fetal brain and heart. Hum Mol Genet 4:1935–1944.

Gardiner PA. 1967. Visual defects in cases of Down's syndrome and in other mentally handicapped children. Br J Ophthalmol 51:469–474.

Harper PS. 1994. Practical genetic counseling, 4th rev. ed. Cambridge: Cambridge University Press. p 60–61.

Hoefnagel CWM. 1989. Observatielijst ouderwordende bewoners in: oud en zwakzinnig. Mentale retardatie vanuit psychologische optiek. Lisse: Swets & Zeitlinger. p 99–131.

Jacobson L. 1988. Ophthalmology in mentally retarded adults. A clinical survey. Acta Ophthalmol 66:457–462.

Janicki MP, Jacobson JW. 1986. General trends in sensory, physical, and behavioral abilities among older mentally retarded persons. Am J Ment Defic 90:490–500.

Jones KL. 1997. Smith's recognizable patterns of human malformation, 5th ed. Philadelphia: WB Saunders. p 8–13.

Katz J. 1994. Handbook of clinical audiology, 4th ed. Baltimore: Williams and Wilkins. p 283–285.

Kelly JS. 1996. Eye examination and vision testing. Br J Nurs 5:630–634.

Kennerley Bankes JL. 1974. Eye defects of mentally handicapped children. Br Med J 2:533–535.

Kinnell HG, Gibbs N, Teale JD, Smith J. 1987. Thyroid dysfunction in institutionalised Down's syndrome adults. Psychol Med 17:387–392.

Kleczkowska A, Fryns JP, Van den Berghe H. 1990. On the variable effect of mosaic normal/balanced chromosomal rearrangements in man. J Med Genet 27:505–507.

Korenberg JR, Kawashima H, Pulst S-M, Ikeuchi T, Ogasawara N, Yamamoto K, Schonberg SA, West R, Allen L, Magenis E, Ikawa K, Taniguchi N, Epstein CJ. 1990. Molecular definition of a region of chromosome 21 that causes features of the Down syndrome phenotype. Am J Hum Genet 47:236–246.

Kraijer DW, Kema GN. 1990. Sociale Redzaamheidsschaal. Lisse: Swets & Zeitlinger.

Mattei JF, Mattei MG, Baeteman MA, Giraud F. 1981. Trisomy 21 for the region 21q223: identification by high-resolution R-banding patterns. Hum Genet 56:409–411.

Maurizi M, Ottaviani F, Paludetti G. 1995. Objective methods of hearing assessment: an introduction. Scand Audiol 24(Suppl 41):5–7.

McGrother CW, Marshall B. 1990. Recent trends in incidence, morbidity and survival in Down's syndrome. J Ment Defic Res 34:49–57.

Moss SC. 1991. Age and functional abilities of people with a mental handicap: evidence from the Wessex mental handicap register. J Ment Defic Res 35:430–445.

Mul M, Verhaart W, Bierman A. 1997. Slechthorendheid bij mensen met een verstandelijke handicap in de huisartspraktijk. Huisarts Wet 40: 301–304.

Norman MG, McGillivray BC, Kalousek DK, Hill A, Poskitt KJ. 1995. Congenital malformations of the brain. Pathologic, embryologic, clinical, radiologic and genetic aspects. New York: Oxford University Press.

Pueschel SM, Pezzullo JC. 1985. Thyroid dysfunction in Down syndrome. Am J Dis Child 139:636–639.

Pueschel SM, Annerén G, Durlach R, Flores J, Sustrová M, Verma IC. 1995. Committee report. Guidelines for optimal medical care of persons with Down syndrome. Acta Paediatr 84:823–827.

Schneider MJ, Loots GMP, Reuter J. 1990. Kent Infant Development Scale (KID-N). Nederlandse uitgave. Lisse: Swets & Zeitlinger.

Shapiro MB, France TD. 1985. The ocular features of Down's syndrome. Am J Ophtalmol 99:659–663.

Smink M, Eerdmans-Dubbelt SLC, van der Wouden JC. 1992. Medische problemen van verstandelijk gehandicapten in een gezinsvervangend tehuis. Huisarts Wet 35:461–464.

Stinissen J. 1965. Terman-Merrill Intelligentieschaal-Vorm L-M. Uitgegeven door de Faculteit der Psychologie en Pedagogische Wetenschappen. Katholieke Universiteit Leuven.

Stinissen J, Vander Steene G. 1970. WPPSI: Wechsler preschool and primary scale of intelligence. Handleiding bij de Nederlandse aanpassing. Lisse: Swets & Zeitlinger.

Thase ME. 1982. Longevity and mortality in Down's syndrome. J Ment Defic Res 26:177–192.

Trommelen J, De Bal C. 1994. Prevalentie van slechthorendheid in een geïnstitutionaliseerde populatie verstandelijk gehandicapten zonder Down syndroom. Logopedie (7)2:29–32.

Van Buggenhout GJCM, Hamel BCJ, Trommelen JCM, Mieloo H, Smeets DFCM. 1994. Down-Turner syndrome: case report and review. J Med Genet 31:807–810.

Van der Meulen BF, Smrkovsky M. 1983. Bayley Scales of Infant Development. Nederlandse Uitgave (BOS 2-30). Lisse: Swets & Zeitlinger.

Van Haasen PP, Vander Steene G, De Bruyn EEJ et al. 1986. Wechsler intelligence scale for children-revised, Nederlandse uitgave. Lisse: Swets & Zeitlinger.

Verpoorten RA, Emmen JG. 1995. A tactile-auditory conditioning procedure for the hearing assessment of persons with autism and mental retardation. Scand Audiol 24(Suppl 41):49–50.

Walsh SZ. 1981. Keratoconus and blindness in 469 institutionalised subjects with Down syndrome and other causes of mental retardation. J Ment Defic Res 25:243–251.

Warburg M. 1982. Why are the blind and severely visually impaired children with mental retardation much more retarded than the sighted children? Acta Ophthalmol Suppl 157:72–81.

Warren AC, Holroyd S, Folstein MF. 1989. Major depression in Down's syndrome. Br J Psychiatry 155:202–205.