A systematic genetic-etiological survey in a Dutch population of institutionalised mentally retarded patients

Diagnostic investigations and implications for medical care

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Diagnostic investigations and implications for medical care

Een wetenschappelijke proeve op het gebied van
de Medische Wetenschappen

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Opgedragen aan mijn ouders, Stefaan, Astrid en Maarten.

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1 GENERAL INTRODUCTION

In the beginning of the twentieth century, Sir Francis Galton considered intelligence as a single hereditary entity, regulating cognitive processing which could be measured through biological tests (e.g. the reaction test). Alfred Binet developed in 1905 a method to measure intelligence, which is now a standard. William Stern introduced the term intelligence quotient (IQ), which is the ratio between mental age (MA) and chronological age (CA), 100 times multiplied (IQ=(MA/CA)*100) (Eysenck and Evans 1996). The IQ is generally subdivided into verbal and performance tasks. The IQ in the population follows approximately a normal Gaussian distribution, with population mean μ=100 and standard deviation sigma=15 (Dumont 1980).

1.1 DEFINITION AND CLASSIFICATION OF MENTAL RETARDATION

Mental retardation (MR) is a lifelong human disability characterised by impaired cognitive and adaptive skills. The definition of MR is difficult to formulate since several categories of impairment are involved.

The most widely used definition, was proposed by the American Psychiatric Association (1994) and 3 criteria were included: 1. Significantly sub-average general intellectual functioning (IQ=< 70), 2. Significant limitations in adaptive functioning in at least two of the following skill areas: communication, self care, ability to live independently, social and interpersonal skills, use of public services, decision taking, functional academic skills, work, leisure, health and safety, 3. Onset before age 18 years.

On basis of the IQ level, several subclasses are distinguished. Assuming that IQ is a normally distributed continuous variable, with population mean of 100 and standard deviation of 15, MR may be classified within approximate IQ ranges as mild in the range 50 to 70 (-2.0 to -3.3 SD), or severe when the IQ is less than 50 (WHO, 1985). Table 1 presents an historical overview of MR classification. The classification of the World Health Organisation (WHO, 1980) and of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV; American Psychiatric Association, 1994) are currently most used (Table 2). Besides the intellectual impairment, the DSM IV takes the adaptive behaviour into account.

Table 1: Historical overview of the classification of the mental level

1948 terminology (WHO)	1968 terminology (WHO)	IQ level (WHO criteria, 1980)	IQ level (DSM IV, 1994)
Borderline	Borderline	70 to 85	70 to 85
Feebleminded/moron	Mild	50 to 70	50-55 to 70
Low degree imbecile	Moderate	35 to 50	35-40 to 50-55
High degree imbecile	Severe	20 to 35	20-25 to 35-40
Idiot	Profound	< 20	<20-25

1.2 PREVALENCE AND SEX DISTRIBUTION OF MENTAL RETARDATION

In Europe and the USA it is generally accepted that MR occurs in 2% to 3% of the general population (Schaefer and Bodensteiner, 1992; Pulsifer, 1996). About 85% are mildly, 10% moderately, 3 to 4% severely and 1 to 2% profoundly mentally retarded (DSM IV, American Psychiatric Association, 1994). A lower prevalence of MR of 1 to 1.5% was reported by Claes (1997), Matilainen et al (1995) (1.38%), Baird and Sadovnik (1985) and Turner (1996).

Mild MR is estimated to occur at 20 to 30 per 1000 and severe MR at 3 to 4 per 1000 (Schaefer and Bodensteiner, 1992). Roeleveld et al (1997) critically reviewed the literature on the prevalence of MR, and concluded that the most likely prevalence of MR is 3% in school aged children. The prevalence rate for severe MR (IQ of =<50) varies around value of 3.8 per 1000 (Roeleveld et al 1997), and this agrees with the WHO rate of 3 to 4 per 1000 (WHO 1986,1968). The prevalence rate for severe MR is age dependent: up to the age of 15 years there is an increasing prevalence, indicating that severe MR is not fully assessed in the first years of life. Prevalence estimates for mild mental retardation varies more widely with a range of 0.4 to 8.0%, which is too wide to allow valid conclusions, and the "true" average prevalence of mild MR was calculated 29.8 per 1000 in school-aged children (Roeleveld et al 1997). This value agrees with the WHO overall figure of 3% for MR (WHO 1986, 1968).

Maas et al (1988) studied the prevalence rates of MR in the Netherlands and found that both mild (IQ>50) and severe (IQ=<50) MR were 0.4%.

According to Roeleveld et al (1997), the male to female ratio in severe MR shows an excess of males of 20% (male to female ratio = 1.20), probably due to

sex-linked genetic factors. In mild MR, the male to female ratio ranges from an excess of males of 40 to 80% (male to female ratio: 1.40-1.80) (Roeleveld et al 1997). In the Netherlands, the male to female ratio in Dutch pupils, under the age of 12 years, decreases with increasing severity of MR (Hamel 1999). In schools for children who need special education for specific educational needs the male to female ratio is estimated 2.73, in schools for children with learning difficulties 1.60, and in schools for children with severe learning difficulties 1.54. In institutions for mentally handicapped the male to female ratio is estimated 1.37 (Hamel 1999).

1.3 ETIOLOGIC RESEARCH IN MENTAL RETARDATION: A CHALLENGE

1.3.1 Etiological studies

The search for the etiology of MR is difficult and represents a continuous challenge for clinicians and other professionals in this field. Both genetic and environmental factors can cause MR.

Recently, Curry et al (1997) evaluated the rational approach to the individual with MR and formulated the recommendations of the American College of Medical Genetics: 1. The individual with mental retardation, the family, and medical care-providers benefit from a focused clinical and laboratory evaluation aimed at establishing causation and in providing counselling, prognosis, recurrence risks, and guidelines for management. 2. Essential elements of the evaluation include a three-generation pedigree, pre-, peri-, and post-natal history, complete physical examination focused on the presence of minor anomalies, neurological examination, and assessment of the behavioural phenotype. 3. Selective laboratory testing should, in most patients, include a banded karyotype. Fragile X testing should be strongly considered in both males and females with unexplained mental retardation, especially in the presence of a positive family history, a consistent physical and behavioural phenotype and absence of major structural abnormalities. Metabolic testing should be initiated in the presence of suggestive clinical and physical findings. Neuro-imaging should be considered in these patients without a known diagnosis especially in the presence of neurological symptoms, cranial contour abnormalities, microcephaly, or macrocephaly. In most situations MRI is the testing modality of choice. 4. Sequential evaluation of the patient, occasionally over several years, is often necessary for diagnosis, allowing for delineation of the physical and behavioural phenotype, a logical approach to ancillary testing and appropriate prognostic and reproductive counselling.

Several large systematic etiological surveys concluded that the cause of MR remains

Table 2: Overview of published systematic etiological surveys

Study	Number	Level MR	Unknown	Chromosomal (Down syndrome) (1)
Czeizel et al 1980	1364	Mild/mod/ severe	172 (12.6%)	72 (5.3 %) (47 (3.4 %))
Thoene et al 1981	727	Moderate/ severe	ND	72 (9.9%) (42 (5.8 %))
Fryns et al 1986	173	Severe	20 (11.56%)	26 (15.1%) (22 (12.7%))
Dereymaeker et al 1988	158	Mod/severe	29 (18.4%)	21 (13.3%) (14 (8.9%))
Fryns et al 1990	262	Moderate	80 (30.5%)	46 (17.5%) (43 (16.4%))
Fryns et al 1990	114 (52F)	Mod/severe	35 (30.7%)	26 (22.8%) (20 (17.5%))
Volcke et al 1990	274 (0F)	Moderate	142 (51.8%)	9 (3.3%) (4 (1.5%))
Haspeslagh et al 1991	307 (0F)	Severe	180 (58%)	23 (7.4%) (19 (6.2%))
Volcke et al 1991	57 (44F)	Mild/border-line	31 (54.4%)	1 (1.8%) (0)
Farag et al 1993	400	Severe (IQ<50)	40 (10%)	37 (9.25%) (34 (8.5%))
Temtamy et al 1994	116	Borderline/ mild/severe	32 (27.6%)	4 (3.4%) (3(2.6%))
Schaap et al 1995	116	Mod/severe	59 (50.9%)	11 (9.5%) (7 (6%))
Claes 1997	454 (166F)	Mild/mod	318 (84%)	21 (6%) (7 (1.5%))
Devriendt et al 1998	66 (19F)	Mild/mod/ severe	32 (48.5%)	22 (33%) (19 (29%))
Félix et al 1998	202	Severe/Mild	70 (34.65%)	69 (34.2%) (65 (32.15%))
Lantigua-Cruz et al 1999	512 (206F)	Severe	66 (12.9%)	213 (41.6%) (205 (40%))

(1) Total number of patients with a chromosomal abnormality, including Down syndrome. (): number of patients with Down syndrome.

(2) Number of patients with idiopathic MR and with a positive family history of non-specific MR.

(3) Number of patients with idiopathic MR and with family data compatible with X-linked MR.

F: number of females.

Monogenic disorders	MCA/MR	CNS	Acquired	(2)Unknown MR / nonspec fam MR	(3) Unknown MR / X-L fam MR
96 (7%)	-	-	396 (29%)	540 (39.6%)	ND
30 (4.1%)	ND	ND	ND	ND	ND
34 (19.5%)	7 (4%)	8 (4.6%)	75 (43.4%)	9 (5.2%)	-
36 (22.8%)	8 (5.1%)	6 (3.8%)	51 (32.3%)	7 (4.4%)	ND
44 (16.8%)	5 (1.9%)	4 (1.3%)	83 (31.7%)	24 (9.2%)	11 (4.2%)
21 (18.4%) 3 FRAXA	4 (3.5%)	1 (0.9%)	27 (23.7%)	18 (15.8%)	3 (2.6%)
44 (16%)	5 (1.8%)	9 (3.3%)	65 (23.7%)	22 (8%)	22 (8%)
43 (13.9%)	6 (1.9%)	-	57 (18.4%)	53 (17.3%)	13 (4.2%)
3 (5.3%)	-	-	23 (40.4%)	ND	6 (10.5%)
137 (34.25%)	22 (5.5%)	7 (1.75%)	175 (39.25%)	ND	ND
13 (11.2%)	28 (24.1%)	15 (12.9%)	6 (5.2%)	ND	ND
16 (13.8%)	4 (3.4%)	-	26 (22.4%)	6 (5.2%)	3 (2.6%)
39 (10%)	-	-	-	46 (10.1%)	23 (5.1%)
4 (6%) 4 FRAXA	2 (3%)	3 (4.5%)	3 (4.5%)	5 (7.6%)	2 (3%)
25 (12.37%)	8 (3.96%)	8 (3.9%)	21 (10.39%)	8 (4%)	-
28 (5.5%)	ND	5 (0.9%)	200 (39%)	ND	ND

Table 3: Overview of systematical surveys with attention to cytogenetic abnormalities

Study	Number	Mental level	Chromosomal (Down syndrome)	Remarks
Mounoud et al 1976	82 (39F)	Mild/Profound	25 (30.5%) (18 (22%))	
Speed et al 1976	2770 (1205F)	MR	297 (10.7%) (250 (9%))	
Sutherland G 1976	588 (258F)	Borderline/Profound	90 (15.3%) (73 (12.4%))	
Jacobs et al 1978	475 (191F)	Borderline/Profound	57 (12%) (40 (8.4%))	
Ally and Grace 1979	512 (136F)	MR	57 (11.1%) (42 (8.2%))	
Gripenberg et al 1980	1062	MR	350 (33%) (305 (28.7%))	
Kondo et al 1980	449 (188F)	Mild/Profound	37 (8.1%) (33 (7.3%))	
Nelson and Smart 1982	720 (?F)	MR	148 (20.5%) (127 (17.6%))	
Brøndum-Nielsen et al 1983	476 (227F)	Mild/Profound	76 (16%)) (58(12.2%))	2 (0.4%) FRAXA
Fryns et al 1984	1991 (937F)	Moderate/Severe	423 (21.2%) (295 (14.8%))	57 (2.9%) FRAXA
Schreppers-Tijdink et al 1988	1170 (449F)	Severe/Profound	258 (22.1%) (167 (14.3%))	21 (6.8%) FRAXA
English 1989	512 (0F)	MR	110 (21.5%) (65 (12.7%))	30 (5.9%) FRAXA

F: number of females

unknown in about 50% (variation from 10% to 84%) of the individuals (Tables 2 and 3). In severe MR a single factor can be identified in more than 50% of the cases. In mildly mentally retarded patients an etiological factor is found in less than 20%, but there is an increased incidence of familial MR. Also, persons from socially disadvantaged backgrounds are over-represented in mild MR (Crow and Tolmie 1998).

1.3.1.1 Chromosomal abnormalities

Chromosomal abnormalities are the most recognisable common cause of severe MR. Down syndrome or trisomy 21 is the most frequent chromosomal abnormality

and accounts for 2/3 of the chromosomal abnormalities associated with MR. Structural chromosomal abnormalities are more rare. Routine chromosomal studies include GTG-banding techniques on metaphases of cultured peripheral lymphocytes. Additional chromosomal banding techniques include reverse-, C- and Q-banding techniques on metaphases or prometaphases (high resolution banding techniques) on cultured peripheral lymphocytes or other cultured tissue cells. Molecular cytogenetic techniques (Fluorescence in situ hybridisation; FISH) are complementary to detect submicroscopic interstitial or subtelomeric deletions and cryptic translocations.

Diagnosis of numerical or structural chromosomal abnormalities has an important impact on genetic counselling, as they may be the unbalanced result of a chromosomal rearrangement, such as a translocation or inversion, in one of the parents.

1.3.1.2 Monogenic disorders

Mutations in one single gene account for 20 to 25% in severe and for 5 to 10% in mild MR (Hamel and Smeets 1997). New laboratory techniques have recently become available to study metabolic disorders e.g. Smith-Lemli-Opitz syndrome and Congenital Disorders of Glycosylation (Jaeken syndrome, carbohydrate-deficient glycoprotein syndrome, CDG syndrome). The study of MR in combination with dysmorphic features has resulted in the delineation and recognition of an increasing number of so called MCA/MR syndromes. With the advent of molecular biology many of the underlying disease genes have been identified, and mutation analysis is now available for diagnosis, and genetic counselling of the families.

X-linked mental retardation (XLMR) is estimated to affect 20 to 25% of all mentally retarded males and 10% of mildly mentally retarded females (Turner 1996; Turner and Turner 1974). XLMR conditions are categorised as syndromic (MRXS), when associated with characteristic clinical features, or non-specific (MRX), when no clinical features other than MR are present. The most frequent disorder in the group of MRXS is the fragile X syndrome (FRAXA), which accounts for about 15 to 20% of all male XLMR patients (Claes 1997; Stevenson 2000). In MRX, which accounts for two thirds of all XLMR, only 8 genes have been identified until now, and these account each for only 0.5 to 1% of all MRX patients (Chelly, 2000; Carrié et al, 1999; Zemni et al, 2000; Merienne et al, 2000; Kutsche et al, 2000; D'Adamo et al, 1998; Billuart et al, 1998; Allen et al, 1998; Gecz et al, 1996; Gu et al, 1996).

1.3.1.3 CNS malformations

Previous studies showed low percentages of MR patients with CNS malformations, the figures varying between 0.9% and 12.9%. This probably represents an underestimate due to the small proportion of patients who received brain-imaging studies.

1.3.1.4 Acquired disorders

Acquired disorders include pre-, peri- or postnatal events such as trauma, toxic agents or infections. Most probably, they account for 30 to 35% of patients with severe and 15% of patients with mild MR (Hamel and Smeets 1997).

1.3.1.5 Idiopathic MR

In about 50% of patients the etiology of MR remains unknown. In the group of patients with severe MR this percentage is estimated as 20% and in mild MR as 80 to 85%. In this group of patients with idiopathic MR, familial non-specific MR was estimated between 4% and 39.6% (Table 2). The percentages of patients with idiopathic MR and family data compatible with X-linked MR, with no affected females and no father-to-son transmission, were between 2.6% and 10.5% (Table 2).

1.3.2 Aim of the present study

For many years, etiological research in mental retardation, and especially in X-linked mental retardation, has been a specific interest at the Centres for Human Genetics in Nijmegen and Leuven-Maastricht. These resulted in several PhD theses (Nijmegen: Renier 1983, Smeets 1992, Smits 1996, van der Maarel 1997, Hamel 1999; Leuven-Maastricht: Fryns 1986, Curfs 1989, Borghgraef 1991, Maes 1993, Schrander-Stumpel 1995, Claes 1997).

The first aim of this thesis was to record etiological diagnoses explaining the cause of the mental handicap in all residents, by means of a systematic genetic-etiological survey, of the institution "Huize Assisië", according to the present knowledge of dysmorphology and technical investigations, including standard cytogenetic, molecular and biochemical techniques. After the systematic screening, a group of patients was selected, to study subtelomeric chromosomal rearrangements with new molecular cytogenetic techniques. Two metabolic disorders were further studied in selected groups of patients using new techniques (Smith-Lemli-Opitz and CDG syndromes). Since the majority of residents in this institution were males, a selected group of male patients was included in the

research project on X-linked mental retardation of the European XLMR Consortium (Chelly J (Paris), Fryns J-P (Leuven), Hamel B (Nijmegen), Moraine C (Tours), Ropers H-H (Berlin), Mandel J-L (Illkirch)). Especially in the group of male patients with so called idiopathic MR, data on familial occurrence of MR, dysmorphic findings, neurological abnormalities and abnormal biometric data were recorded.

The second aim of this study was the determination of medical complications, the long-term follow-up and prognosis in the different diagnostic subgroups (i.e. chromosomal disorders, X-linked mental retardation, inborn errors of metabolism, and dysmorphology-mental retardation syndromes). In addition, the general practitioners of this institution often received questions from family members, who asked for genetic counselling. In this institution most residents were older mentally retarded adults. The phenotypical presentation of most syndromes is well known in children, but with advancing age features may change, which renders the clinical diagnosis more difficult. New medical complications may occur in older age groups, and these are often not well described in the literature. Therefore, there was need for adequate strategies to prevent these medical complications. A reliable diagnosis can be of help in intervention planning, which includes the provision of procurement of essential services resulting in increased independence, productivity and community integration (Schalock et al 1994). It was thus justified to extensively investigate each resident.

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2 MATERIALS AND METHODS

2.1 PATIENTS

A systematic diagnostic-etiological survey was started in 1992 in the institution "Huize Assisië - Stichting Prisma". This is located in the southern central part of the Netherlands and was founded in 1904 when 21 mentally retarded males accompanied by 4 Fathers "Penitenten" arrived at Biezenmortel, The Netherlands (Bouwens and Hoek 1994). Historically, only male patients were living in the institute. Presently 591 patients (mean age: 46 years) live in the institution, 552 males (93.4%) (mean age: 47 years) and 39 females (6.6%) (mean age: 33 years). Table 1 presents an overview of the age distribution and sex distribution. Table 2 presents an overview of the level of MR according to age and sex.

Table 1: Distribution of age and mean age of the patients

Age (years)	Number of males (n)	Mean age males (years)	Number of females (n)	Mean age females (years)	Total (n)	Mean age (years)
0 - 9	1	8	1	3	2 (0.3%)	6
10 - 19	11	15	7	14	18 (3.05%)	15
20 – 29	20	25	7	25	27 (4.6%)	25
30 – 39	81	34	15	35	96 (16.2%)	34
40 – 49	188	45	3	44	191 (32.3%)	45
50 – 59	193	54	4	55	197 (33.3%)	54
60 – 69	49	63	2	64	51 (8.6%)	63
70 – 79	8	72	-	-	8 (1.4%)	72
>= 80	1	80	-	-	1 (0.3%)	80
Total	552 (93.4%)	47	39 (6.6%)	33	591	46

Table 2: Distribution of mental level according to age and sex

Age (years)	Borderline	Mild	Moderate	Severe	Profound	Total (n)
0 – 9 M	-	-	-	-	1	1
0 – 9 F	-	-	-	-	1	1
10 – 19 M	-	1	4	4	2	11
10 – 19 F	-	1	-	2	4	7
20 – 29 M	-	2	9	9	-	20
20 – 29 F	-	5	2	-	-	7
30 – 39 M	-	21	41	14	5	81
30 – 39 F	3	6	5	-	1	15
40 – 49 M	1	25	60	51	51	188
40 – 49 F	-	1	2	-	-	3
50 – 59 M	1	23	63	57	49	193
50 – 59 F	-	2	2	-	-	4
60 – 69 M	-	8	25	7	9	49
60 – 69 F	-	2	-	-	-	2
70 – 79 M	1	2	4	1	-	8
70 – 79 F	-	-	-	-	-	-
>= 80 M	-	-	1	-	-	1
>= 80 F	-	-	-	-	-	-
Totals M	3 (0.5%)	82 (14.9%)	207 (37.5%)	143 (25.9%)	117 (21.2%)	552
Totals F	3 (7.7%)	17 (43.6%)	11 (28.2%)	2 (5.1%)	6 (15.4%)	39
Total	6 (1.02%)	99 (16.8%)	218 (36.9%)	145 (24.5%)	123 (20.8%)	591

M: males
F: females

2.2 METHODS

2.2.1 Selection of patients and general procedure

The medical records of each patient were studied and data on family history and pedigree, pre-, peri- and postnatal period, psychomotor development and mental functioning, early medical history, medical complications, vision and hearing and specialised clinical examinations and technical investigations were collected.
A different strategy was used for 1. residents with the clinical diagnosis of Down syndrome and 2. without Down syndrome.

2.2.1.1 Residents with the clinical diagnosis of Down syndrome (n=96)

The medical records of these residents were studied, to record whether chromosomal studies were performed to rule out an inherited type of trisomy 21. Data on mental functioning, dementia, neurologic abnormalities, epileptic seizures, ophthalmologic and hearing functioning and thyroid function were collected. In 40 DS patients (38 males and 2 females), chromosomal studies had been performed in the past. In the group of 56 residents without chromosomal studies, a written permission to obtain blood for cytogenetic studies was asked of the parents or the legal representative. When there was no permission to collect blood, no investigations were performed. If there was no reaction within 3 months to the first request, a second letter for permission was sent. In 47 of these 56 residents, the parents or the legal representative consented to blood samples being taken and cytogenetic studies being performed. A written report of the result was sent to the family. In the case of a translocation type of trisomy 21, the family was investigated and counselling was given.

2.2.1.2 Residents without Down syndrome (n=495)

In 63 patients (61 males and 2 females) the diagnosis made in the past was re-evaluated. In the group of patients without a diagnosis a written permission to participate in the study, together with a questionnaire, asking for anamnestic and family data, was sent to the parents or to the legal representative. Based on data from the medical records, an attempt was made to establish the most likely etiological diagnosis. When there was no permission to participate in the present study, no further investigations were performed. If there was no reaction on the first request within a period of 3 months, a second, more detailed request was sent. As soon as a written permission was received, patients were clinically examined. Blood and urine samples were obtained for cytogenetic studies and metabolic screening. Molecular studies of the FMR-1 gene were performed, based on clinical phenotype and family data in a selected group of patients (n=244). When a definitive diagnosis could not be established, the family or legal representative was informed on all performed investigations in a standardised letter. When a diagnosis was found, parents or family members were invited to the institution for counselling, and the results were summarised in a written report. Families were visited and investigated in the group of patients with chromosomal abnormalities, X-linked mental retardation and metabolic disorders.

Written consent for the publication of clinical photographs and clinical and technical data, was obtained from the parents or legal representative.

The 591 patient records were studied in detail. In 103 residents (17.4%) (40 residents with Down syndrome and 63 with another diagnosis) a diagnosis previously made was re-evaluated. Four patients died before the investigation was started. In 32 patients there was no reaction from parents or legal representative and therefore no investigation was performed. In another 84 patients no permission was given. Finally, 471 residents (436 males and 35 females) participated in the present study and could be investigated.

2.2.2 Methodology

2.2.2.1 Mental functioning

The educational psychologists of the institution performed studies on mental level in all patients (Table 2). Several psychological tests, adapted for the Dutch population, were used, depending on the level of mental functioning. In the 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 Pre-school 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 used 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 existing of 5 sub-scales including cognition, motor development, language, personal autonomy and social skills. The second test used was the Bayley Developmental Scale (BOS 2-30) (Van der Meulen and Smrkovsky 1983) which includes a mental and a motor scale. The third test was the Terman-Merrill Intelligence Scale (Stinissen 1965) in which cognition between the ages of 2 and 22 years can be tested. The patients were 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 behaviour (Vineland Adaptive Behavior Scales (Sparrow et al 1984) and Sociale Redzaamheidsschaal voor Zwakzinnigen (SRZ) (Kraijer and Kema 1972) of the individual were used to classify patients.

2.2.2.2 Clinical examination

A standard clinical examination was performed by the same clinician (Van Buggenhout G). The results in all patients were discussed with Hamel B (Nijmegen) and some of the patients were selected for further discussion with the medical staff in Nijmegen and Leuven. A selected group of patients was observed and clinically examined at the institution (Hamel B (Nijmegen) and Fryns J-P (Leuven)).
Biometric data on height, arm span, weight and head circumference, outer canthal distance (OCD), inner canthal distance (ICD), ear length, total hand length (THL) and palm length (PL) and testicular volume were recorded. Clinical examination included the general habitus of the patient, inspection of skin, craniofacial features, and examination of the upper and lower extremities, thorax, abdomen, back and genitalia. A standard neurological examination was performed. Five standard clinical photographs were taken of each patient.

2.2.2.3 Cytogenetic, molecular and metabolic investigations

The laboratory technician of the institution obtained blood of the patients. Cytogenetic studies and DNA studies were done at the laboratories of the Department of Human Genetics, University Medical Center St Radboud Nijmegen, The Netherlands. Metabolic screening was performed at the Laboratory of Paediatrics and Neurology, University Medical Centre St Radboud, Nijmegen, The Netherlands. Cytogenetic studies were performed in all 471 residents on cultured peripheral lymphocytes, according to standard methods, and included GTG-banding techniques. In a selected group of the patients DNA-studies for the FMR-1-gene were performed. In a selected group of patients DNA studies for other diseases (myotonic dystrophy, Kallman syndrome and Tuberous sclerosis) were performed. Metabolic studies were performed in 306 patients and included analysis of amino acids, organic acids, purines and pyrimidines, oligosaccharides, mucopolysaccharides and neuraminic acid. Because it was impossible to obtain 24 hours collection of urine in mentally retarded residents, urinary metabolic studies were performed on samples obtained in the early morning. Additional studies for Smith-Lemli-Opitz syndrome (6 patients) and Jaeken syndrome (Congenital Disorders of Glycosylation; CDG syndrome) (144 patients) were performed in a selected group of patients after the study period. Therefore, it was not possible to investigate material of all initially investigated patients.

2.2.2.4 Additional examinations and investigations

Some patients required specialist examination, e.g. neurological, ophthalmologic, dermatological, or cardiological examination. In some patients

additional technical investigations were performed such as cerebral MRI or computed tomography scan, X-rays of the skull, skeleton or hands, investigation of hairs by electron microscopy, audiometric and ophthalmologic investigations, skin examination by Woods-lamp or specialised metabolic investigations including lactate, ammonia or screening for urinary homocystine. These additional medical and technical investigations were performed after discussion of the medical data of each patient with the different staff members.

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Part 1

General overview of the results of the present study

Content Part 1

Clinical etiological survey of a population of 471 mentally retarded patients living in an institution in the southern part of the Netherlands. (Community Genet, accepted)

CLINICAL ETIOLOGICAL SURVEY OF A POPULATION OF 471 MENTALLY RETARDED PATIENTS LIVING IN AN INSTITUTION IN THE SOUTHERN PART OF THE NETHERLANDS

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ABSTRACT

Objective: Investigation of etiological factors in mental retardation. ***Methods:*** In 471 adults (mean age 46 years; 92.6% males) living in an institution for the mentally retarded, clinical examination, cytogenetic and molecular studies and basic metabolic screening were performed. ***Results:*** Chromosomal abnormalities were found in 100 patients (21.2%). Of these, 87 were numerical autosomal abnormalities (all Down syndrome), 7 structural autosomal abnormalities and 6 numerical abnormalities of sex chromosomes.

Monogenic disorders were diagnosed in 61 patients (13%): 14 autosomal dominant, 25 autosomal recessive and 22 X-linked conditions. In 1.7% (n=8) of the patients a central nervous system (CNS) malformation was documented. Acquired CNS disorders were diagnosed in 69 patients (14.6%): a prenatal cause was found in 15 patients, a perinatal and postnatal cause in each of 27. In 233 patients (49.5% of the total sample; 215 males and 18 females) idiopathic mental retardation was present. In this group there were 2 patients with a high degree of consanguinity (incest). In one third (n=73; 31.3%) of these patients there was a family history of mental retardation (MR in first and second-degree relatives). Pedigree data were most compatible with X-linked mental retardation in 35 males from 32 different families, i.e. 47.9% of the patients with idiopathic MR and family history of MR, and 15% of the total group of patients with idiopathic MR. Thus, X-linked inheritance was considered in a total group of 57 males, accounting for 12.1% of the total population: X-linked disorders in 22 males and non-specific X-linked mental retardation in 35 males. Minor anomalies were present in 41 patients (17.6%). Their presence was significantly associated with the severity of the MR.

Neurological abnormalities were present in 47 patients (20.2%), with central nervous system dysfunction (central paresis, dyskinesia, ataxia) in 45 (19.3%). Seizures were present in one third of the patients (n=78) and a statistically significant correlation between the level of MR and the presence of seizures was found. In the group of males with idiopathic MR, the number of males with the combination of microcephaly and micro-orchidism was higher than expected, but not statistically significant and the number of males with the combination of macrocephaly and macro-orchidism was statistically significantly increased (n=5; 2.3%). Before systematic evaluation, only 21.8% (103/471) of the patients had a known diagnosis. After this survey, 50.5% (238/471) of the investigated patients had a definite diagnosis. ***Conclusion:*** Establishing the diagnosis in older mentally retarded patients is important in the prevention of medical complications and in the development of management strategies of the institution. Finally, it is the conditio sine qua non for genetic counseling of the respective families.

INTRODUCTION

Mental retardation (MR) affects about 2 to 3% of the population [1, 2]. The institution "Huize Assisië, Stichting Prisma" is located in the southern part of the Netherlands. Historically, only male patients were admitted to the institute. Presently, 6.6% of the 591 residents are female. The institute is open to all persons who are not able to function independently in society because of mental retardation. Some of the patients are living outside the institute in small home groups integrated in the community.

The aim of the study was to perform a systematic etiologic-diagnostic survey of all residents. It was hoped that an accurate diagnosis would allow prediction of prognosis and prevention of complications at an older age and offer the possibility of genetic counselling to the respective relatives.

MATERIALS AND METHODS

Patients

At the time of the study 591 adults (552 males (93.4%) and 39 females (6.6%)) were living in the institution. Only 471 patients were investigated, since 4 patients died before the investigation was performed and in 116 patients no permission was obtained.

Mental functioning

Educational psychologists of the institution tested all residents to determine the level of intellectual functioning. Several psychological tests adapted to the Dutch population were used. 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) [3] was used. The Wechsler Primary Pre-school Scale of Intelligence test (WIPPSI) [4] 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 used 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) [5], a developmental scale between 1 and 14 months existing of 5 sub-scales including cognition, motor development, language, personal autonomy and social skills. The second test used was the Bayley Developmental Scales (BOS 2-30) [6] and included a mental scale and motor scale. The third test was the Terman-Merrill [7] in which cognition between the ages of 2 years and 22 years can be tested. The patients were classified according to the criteria described in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) [8]. Both the intellectual impairment and the adaptive behavior of the individual were used to classify patients.

Clinical examination

After permission was obtained, all patients were examined clinically according to a standard checklist, including also biometric values, such as length, weight, head circumference, outer canthal distance, inner canthal distance, total hand length, finger-III-length, ear length, and testicular volume. The family history was obtained by a questionnaire which had to be filled out by the parents or family of the patient. These data were completed by data present in the clinical file. The occipito-frontal circumference (OFC) was defined in males with 3rd centile=53 cm and 97th centile=58 cm and in females 3rd centile=52 cm and 97th centile= 56.5 cm [9, 10]. Bushby et al. [11] reported a correlation between height and head circumference in 354 healthy control individuals and stated that the P-values for the head circumference should be adapted to height. The centile charts used routinely have data only up to age 16 years and therefore Bushby et al. [11] produced centile charts appropriate for use in adults. In the group of males the OFC (after correction for height) was compared with the testicular volume. Macro-orchidism was defined as a testicular volume $\geq$ 25 ml and micro-orchidism as a testicular volume $\leq$ 10 ml

[12]. MR in one or both parents, one or more sibs, or children was considered first degree familial MR. In second degree familial MR one or more uncles or aunts, nieces or nephews were mentally retarded. A third group comprised MR in third degree relatives (cousins), but this group was not taken into account for familial MR, since detailed information on these relatives was lacking. The patients were discussed with at least 2 experienced clinical geneticists.

Cytogenetic studies

Cytogenetic studies on cultured peripheral lymphocytes included G-banding techniques, according to standard procedures. In 4 patients, additional chromosomal studies on cultured fibroblasts were performed for somatic mosaicism (Wolf-Hirschhorn syndrome and Pallister-Killian syndrome (3 patients)), or to confirm Down-Turner mosaicism syndrome (1 patient).

Molecular studies

On the basis of the clinical findings and pedigree data, molecular studies were performed and included DNA screening of the fragile X syndrome with CGG expansion in the FMR1 gene in 244 patients.

Metabolic screening tests

Metabolic screening tests included urine and blood screening for amino acids (n=306), urine for organic acids, oligosaccharides and mucopolysaccharides, and purine and pyrimidine metabolism (n=306). After this systematic screening, in addition 2 metabolic disorders were investigated in a selected group of patients, 6 for Smith-Lemli-Opitz syndrome (criteria: MR and partial syndactyly of 2nd and 3rd toes) and 144 for congenital disorders of glycosylation (CDG) syndrome (criterion: MR of unknown origin).

Neuro-imaging

It was difficult to perform systematic neuro-technical investigations in this population of older mentally retarded patients, since light anesthesia was necessary to obtain a good quality of brain imaging, and because of financial restrictions. Therefore, only 25 patients were selected for magnetic resonance imaging (MRI) (n=14) or computed tomography (CT) (n=11) of the brain (criteria: MR of unknown etiology and complex neurological signs with central paresis (spastic diplegia or quadriplegia) or progressive neurological regression).

RESULTS

Patients

The mean age of the 471 patients was 46 years, ranging from 3 to 75 years. Two-thirds of the patients were between 40 and 59 years of age (table 1).
The sex distribution was 436 males (92.6%) with a mean age of 47 years and 35 females (7.4%) with a mean age of 32 years.

Table 1. Distribution of age and mean age of all 471 patients

Age (years)	Number of males (n)	Number of females (n)	Total (n)	Mean age (years)
0 – 9	-	1	1 (0.2%)	3
10 – 19	6	7	13 (2.8%)	14
20 – 29	17	6	23 (4.9%)	25
30 – 39	62	14	75 (15.9%)	36
40 – 49	159	2	161 (34.2%)	45
50 – 59	153	3	156 (33.1%)	54
60 – 69	36	2	38 (8.1%)	63
70 – 79	3	-	3 (0.6%)	74
Total	436 (92.6%)	35 (7.4%)	471 (100%)	46

Mental functioning

Table 2 presents the level of mental functioning, according to age and sex in all 471 patients. More than 80% of the patients were moderately, severely or profoundly mentally retarded. Almost 50% of the females were borderline to mildly mentally retarded.

Classification of all patients according to diagnosis (table 3)

1. Patients with chromosome rearrangements (n=100 (21.2%))

Table 4 presents an overview of all patients with a chromosomal abnormality. In 75 patients full trisomy 21 (2 females and 73 males) was diagnosed. In 11 patients trisomy 21 mosaicism was found and in one patient an autosomal reciprocal translocation was found in the two euploid cells: 47,XY,+21/ 46,XY,t(11;17)(q13;q25) de novo. In another patient a mosaic pattern of double aneuploidy was present: 45,X/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

Table 2. Distribution of mental level according to age and sex of the 471 patients

Age (years)	Borderline	Mild	Moderate	Severe	Profound	Total (n)
0 – 9 M	-	-	-	-	-	-
0 – 9 F	-	-	-	-	1	1
10 – 19 M	-	-	-	4	2	6
10 – 19 F	-	1	-	2	4	7
20 – 29 M	-	1	8	8	-	17
20 – 29 F	-	5	1	-	-	6
30 – 39 M	-	14	31	13	4	62
30 – 39 F	2	6	5	-	1	14
40 – 49 M	1	20	54	47	37	159
40 – 49 F	-	-	2	-	-	2
50 – 59 M	-	19	45	48	41	153
50 – 59 F	-	1	2	-	-	3
60 – 69 M	-	6	17	5	8	36
60 – 69 F	-	2	-	-	-	2
70 – 79 M	-	1	2	-	-	3
70 – 79 F	-	-	-	-	-	-
>= 80 M	-	-	-	-	-	-
>= 80 F	-	-	-	-	-	-
Totals M	1 (0.2%)	61 (14%)	157 (36%)	125 (28.7%)	92 (21.1%)	436 (92.6%)
Totals F	2 (5.7%)	15 (42.9%)	10 (28.6%)	2 (5.7%)	6 (17.1%)	35 (7.4%)
Total	3 (0.6%)	76 (16.1%)	167 (35.5%)	127 (27%)	98 (20.8%)	471

M: males
F: females

fibroblasts. In one patient a de novo (21;21) translocation was present.

Structural abnormalities of the autosomes (n=7; 7%) included patients with well-known syndromes, 1 patient with trisomy 9p syndrome and 5 patients with a deletion syndrome. The patient with cri du chat syndrome (del(5)(p14.1;pter)) and the patient with 13q deletion syndrome (del(13)(q32.3;qter)) were diagnosed after G-banded chromosome studies. The three patients with microdeletion syndromes (Prader-Willi syndrome, Angelman syndrome and Shprintzen syndrome) were diagnosed after FISH. The patient with a complex translocation between chromosomes 1,6 and 9 (karyotype (FISH): 46,XY,der(1)(pter →q32.1::q43→qter),der(6)(9qter→9q21::1q32→1q43::6p11.1→6q11::6q22→6qter), der(9)(9pter→9q21::6q12?::6p11.1→6pter), was a 54-year-old, profoundly mentally retarded macrocephalic male with epilepsy and behavior problems.

Sex chromosomal abnormalities included only numerical abnormalities. The 50-years-old man with 48,XXYY karyotype was moderately mentally retarded, with myopia and micro-orchidism.

Table 3.The diagnostic classification of the 471 patients.

	Number of patients	
Chromosomal disorders		100 (21.2%)
Autosomal disorders		
Numerical	87	
Structural	7	
Sex-chromosomes		
Numerical	6	
Monogenic disorders		61 (13%)
Autosomal dominant	14	
Autosomal recessive		
Syndromic	9	
Metabolic disorders	16	
X-linked disorders		
Fragile X	16	
Syndromic	2	
Nonspecific	4	
Central nervous system malformations		8 (1.7%)
Acquired disorders (multifactorial)		69 (14.6%)
Prenatal	15	
Perinatal	27	
Postnatal	27	
Idiopathic MR		233 (49.5%)
Total		471 (100%)

2. Patients with monogenic disorders (n = 61 (13%))

Monogenic disorders were diagnosed in 61 patients. Of the 14 (23%) patients with an autosomal dominant condition, 5 had neurocutaneous disorders: Tuberous sclerosis (TS) (n=4) and Sturge-Weber (n=1). Twenty-five (41%) patients had an autosomal recessive disorder: microcephalia vera in 6 and metabolic disorders in 16 patients. XLMR was diagnosed in 22 (36%) patients with FRAXA in 16 patients, XLMR with marfanoid habitus syndrome in 2 and nonspecific XLMR in 4 patients (table 5). The 4 MRX patients included 3 brothers of the family carrying a mutation in the IL-1 receptor accessory protein-like gene, localized on Xp22.1-p21.3 [13] and one male patient member of the MRX44 family [14].

Table 4.Classification of 100 patients with chromosomal abnormalities

Chromosome rearrangements	**number**
1. Autosomes (n=94)	
Numerical abnormalities n = 87	
Down syndrome-full trisomy 21	75
Down syndrome-trisomy 21 mosaicism	11
Down syndrome-de novo (21;21) translocation	1
Structural abnormalities n = 7	
Trisomy 9p	1
Cri du chat syndrome – 46,XY,del(5p)	1
46,XY,del(13)(q32.3;qter)	1
Angelman syndrome – del (15q)	1
Prader-Willi syndrome – del (15q)	1
Velo-cardio-facial syndrome – 46,XX,del (22)(q11)	1
Der(1),der(6),der(9) – complex translocation	1
2. Sex chromosomes (n=6)	
Numerical abnormalities: n = 6	
47,XXY – Klinefelter syndrome	1
47,XYY	1
45,X/46,XY/47,XYY (6/43/1)	1
45,X/46,XY (12/88)	1
48,XXYY	1
45,X/46,XX (6/94)	1
All chromosome rearrangements	100

3. Patients with central nervous system malformations (n = 8 (1.7%))

In 7 males central nervous system malformations were present. Two patients had spina bifida aperta with hydrocephalus, 2 congenital hydrocephalus with cerebellar hemiatrophy in one, and one multicystic encephalomalacia (hydranencephaly). Of the 2 males with corpus callosum agenesis, 1 had minor anomalies with macrocephaly, ptosis and bifid uvula. One female had congenital hydrocephalus with spastic tetraparesis.

Table 5. Classification of 61 patients with monogenic disorders

McKusick catalog number	**Disorder**	**Number of patients**
1. Autosomal dominant inheritance		***N= 14 (23%)***
*191092	Tuberous sclerosis (Bourneville)	4
*135500	Zimmermann-Laband syndrome	1
*160900	Dystrophia myotonica (Steinert disease)	1
122470	Cornelia de Lange – Type 1	1
122470	Cornelia de Lange – Type 2 (mild phenotype)	1
#113650	Branchio-oto-renal syndrome (Melnick-Fraser)	1
#108300	Stickler syndrome	1
#193510	Waardenburg syndrome type 2	1
#101200	Apert syndrome	1
*603543	Limb-mammary syndrome	1
185300	Sturge-Weber syndrome	1
Autosomal recessive inheritance-syndromic		***N= 9 (14.8%)***
229120	Fountain syndrome	1
*262000	Björnstad syndrome	1
277590	Weaver syndrome	1
*251200	Microcephalia vera	2
	Microcephalia vera + diabetes mellitus	2
	Microcephalia vera + short stature	1
	Microcephalia vera + polydactyly	1
Autosomal recessive inheritance-metabolic		***N= 16 (26.2%)***
*261600	Phenylketonuria	5
*252900	Sanfilippo A (MPSIIIA)	1
*253220	Sly disease (MPSVII)	1
*257200	Niemann-Pick type B	1
#239500	GM1 gangliosidosis type III (Adult)	1
*239500	Hyperprolinaemia type 1	3
#220100	Cystinuria	1
*272300	S-sulfocysteinuria	3
X linked inheritance		***N= 22 (36%)***
309550	Fragile X syndrome	15
	Fragile X syndrome + Prader-Willi-like phenotype	1
*309520	Lujan-Fryns syndrome (XLMR-marfanoid habitus)	2
	Nonspecific XLMR	4
Total monogenic disorders		***N= 61***

4. Patients with acquired abnormalities (n = 69 (14.6%)) (table 6)

Prenatal infectious agents (rubella) were present in 2 (2.9%) patients, but infectious agents in the postnatal period (meningitis, encephalitis and systemic sepsis) were the cause of MR in almost one third of these patients (n=22; 31.9%).

Table 6. Distribution of 69 patients with acquired abnormalities according to prenatal, perinatal and postnatal events

Acquired abnormalities	**Number of patients**
1. Prenatal cause	***N = 15 (21.8%)***
Congenital Rubella	2
Ecclampsia	1
Rhesus incompatibility	2
Prematurity	1
Prematurity + dysmaturity	6
Prematurity + placenta praevia	1
Dysmaturity	2
2. Perinatal cause	***N = 27 (39.1%)***
Asphyxia/birth complication	27
3. Postnatal cause	***N = 27 (39.1%)***
Meningitis	10
Encephalitis	11
Sepsis	1
Hemorrhagic bleeding	2
Trauma	3
Total number	***N = 69***

5. Patients with an idiopathic type of mental retardation (n=233 (49.5%))

In the group of 233 patients (49.5%; 215 males and 18 females) without specific diagnosis the following parameters were analyzed: consanguinity, familial occurrence of MR, minor anomalies, neurological symptoms, and the presence/concurrence of macro- and microcephaly and macro- and micro-orchidism.

A. Consanguinity

In 9 patients consanguinity was present, including 2 pairs of sibs. In 2 patients a high degree of consanguinity (brother and sister incest) was present.

B. Familial occurrence of MR

Table 7 presents the degree of mental retardation in the group of patients with idiopathic mental retardation subdivided into familial or sporadic MR. Familial MR (first degree (n=67), second degree (n=6) and third degree (n=22)) was present in 95 patients (40.8%), sporadic MR in 129 (55.4%) and in 9 patients (3.9%) data on familial mental retardation could not be obtained. The group of patients with MR in third degree relatives (cousins) was not taken into account for familial MR.
In the 73 patients (69 males and 4 females) with familial MR, 3 affected male sib pairs were found, with a distinct neurological syndrome in 1 of these sib pairs. In 29 other males pedigree data were compatible with X-linked inheritance.

Table 7. Distribution of the level of mental retardation in the group of 233 patients with idiopathic mental retardation according to familial or sporadic MR

Level MR of Indexpatient	Borderline		Mild		Moderate		Severe		Profound		Total		Total
	F	M	F	M	F	M	F	M	F	M	F	M	
Familial MR													
1. first degree relatives	0	0	2	15	2	29	0	10	0	9	4	63	67
2. second degree relatives	0	0	0	0	0	2	0	3	0	1	0	6	6
3. third degree relatives	0	0	0	3	0	5	0	9	0	5	0	22	22
Sporadic MR	2	0	6	22	3	31	1	35	0	29	12	117	129
No information on familial MR	0	0	2	0	0	3	0	1	0	3	2	7	9
Total	2	0	10	40	5	70	1	58	0	47	18	215	233

F: female
M: male

C. Minor anomalies

Minor anomalies were present in 41 patients (17.6%) (table 8). The degree of MR in this group was significantly more severe than in those without minor anomalies (Chi square = 10.33, 3 degrees of freedom, p=0.016, in contingency table 2x4). The presence of anomalies between patients with and without familial MR

Table 8. Overview of the level of mental retardation and the presence of minor anomalies in all 233 patients with idiopathic MR

Level of mental retardation	Patients with minor anomalies number (%)	Patients without minor anomalies number (%)	Total
Borderline/ Mild	5 (12.2%)	47 (24.5%)	52 (22.3%)
Moderate	14 (34.1%)	61 (31.8%)	75 (32.2%)
Severe	7 (17.1%)	52 (27.1%)	59 (25.3%)
Profound	15 (36.6%)	32 (16.7%)	47 (20.2%)
Total	41 (100%)	192 (100%)	233 (100%)

was not statistically different (Chi square = 0.03, 1 degree of freedom, in contingency table 2x2, p=0.86) (table 9).

Cutis verticis gyrata in combination with mental retardation and normocephaly was noted in 3 patients with non-familial MR.

Table 9. Number of patients with minor anomalies in the group of patients with familial mental retardation (first and second degree relatives) and without familial mental retardation. The patients with third degree relatives (n=22) and the patients with no information on familial data (n=9) were not included

	Familial MR	No familial MR	Total
Minor anomalies	12	20	32
No minor anomalies	61	109	170
Total	73	129	202

D. Neurological findings

1. Epilepsy (table 10)

78 of the 233 patients had seizures (33.5%). A statistically significant correlation between the degree of severity of MR and the presence of seizures was found (Chi square=28.85, 3 degrees of freedom, p=0.00000241, in contingency table 2x4). Seizures were more frequent in the group of sporadic patients (i.e. 46/129; 35.7%) than in the group of patients with familial MR (i.e. 19/73; 26%), but this was not statistically significant (Chi square=1.56, 1 degree of freedom, p=0.21).

Table 10. Epileptic seizures in relation to the mental level in the group of 233 patients with idiopathic mental retardation

Level MR of Indexpatient	Borderline	Mild	Moderate	Severe	Profound	Total	General total
Familial MR							
1. first degree relatives	0	4 (1F)	4	5	3	16 (1F)	67
2. second degree relatives	0	0	1	2	0	3	6
3. third degree relatives	0	0	1	5	4	10	22
Sporadic MR	0	3 (1F)	12	12	19 (1F)	46 (2F)	129
No information on familial MR	0	0	0	1	2	3	9
Total	0	7 (2F)	18	25	28 (1F)	78 (3F)	
General total	2	50	75	59	47		233

F: number of females

2. Neurological findings (table 11)

Neurological abnormalities were present in 47 of the 233 patients (20.2%) with central paresis and/or dyskinesia and/or ataxia in 45 patients. There were 6 males, including 2 sibs, with familial MR and spastic diplegia (n=1) or paraparesis of the lower limbs (n=5); 1 was moderately and 5 profoundly mentally retarded. Three also had minor anomalies and 2 were macrocephalic.

E. Biometric values

Microcephaly was present in 11 of the 215 males (5.1%). Three had both microcephaly and micro-orchidism (1.4%), and 1 had minor facial anomalies. The other 2 had small stature and spastic paraplegia and one had also minor anomalies. Statistical analysis showed no significant difference between the combination of presence of microcephaly and micro-orchidism (Analysis of a single table (2x2): Odds ratio=3.19; Fisher exact test: P-value (1 and 2 tailed): 0.118) although this combination was higher than expected (table 12). There were no males with microcephaly and macro-orchidism. Neurological abnormalities (spastic paraplegia) were present in 4 microcephalic males (1.9%) and 2 had also micro-orchidism.

Macrocephaly was present in 8 (3.7%) males. One of these males had micro-orchidism, minor anomalies and diabetes mellitus. Five macrocephalic males had macro-orchidism (2.3%); 2 had minor anomalies and 2 had severe behavior problems with selfmutilation in one and autism in the other. A significant correlation was found between the combination of macrocephaly and

Table 11. Overview of neurological abnormalities in 47 of the 233 patients with idiopathic mental retardation

	Number of patients with sporadic MR	Number of patients with familial MR	Total number of patients
CNS dysfunction			
1. Central paresis			
Diplegia spastica (LL>UL)	2	1	3
Paraparesis (LL)	11	5	16
Paraparesis (UL)	0	1	1
Quadriplegia (UL=LL)	1	4	5
Hemiplegia	3	1	4
2. Dyskinesia (Extrapyramidal)			
Chorea	2	2	4
Athetosis	1	0	1
Dystonia	1	0	1
3. Ataxia	6	4	10
Basal ganglia abnormalities			
Parkinsonism	1	1	2
Total	**28**	**19**	**47**

UL: upper limbs
LL: lower limbs
CNS:central nervous system

macro-orchidism (analysis of a single table (2x2 contingency: Odds ratio=15.30, Fisher exact test: P value (1 and 2 tailed): 0.00136). In all patients with macrocephaly and/or macro-orchidism the diagnosis of fragile X syndrome was excluded by molecular studies (expansion of the CGG repeat in the FMR-1 gene). Four macrocephalic males had neurological abnormalities, and one had also macro-orchidism. Micro-orchidism with normal OFC was present in 18 patients (8.4%), and macro-orchidism with normal OFC in 25 patients (11.6%).
Microcephaly was present in 3 females (16.7%). One microcephalic female had also mild neurological problems. There were no females with macrocephaly.

Table 12. Relation between head circumference and testis volume in the group of males with idiopathic MR (n=215)

	Micro-orchidism	Macro-orchidism	Normo-orchidism	Total
Microcephaly	3	0	8	11
Macrocephaly	1	5	2	8
Normocephaly	18	25	153	196
Total	22	30	163	215

DISCUSSION

In this study a systematic clinical and diagnostic evaluation was performed on 471 mentally retarded adults. Because of the historical setting of this institution, most of residents were males (93%). The mean age was 46 years, ranging from 3 to 75 years. The relatively advanced age of many patients made it difficult to obtain data on the pre- and perinatal period, early development and medical history. A number of MR syndromes are associated with reduced life expectancy and therefore these syndromes will be less frequently found in the elderly mentally retarded. A third bias was towards a more severe level of mental handicap with more than 80% moderately, severely or profoundly mentally retarded. Borderline or mild mental handicap was present in almost 50% of the females, but in only 14.2% of the male population. None of the patients in this study were part of previous systematical etiological surveys.

In previous surveys of mentally retarded patients, the frequency of chromosome abnormalities ranges from 1.8% to 41.6%, depending on the level of MR of the investigated population, and the proportion of patients with Down syndrome from 0% to 40% (tables 13 and 14). In the present study, a cytogenetic abnormality was present in 100 patients (21.2%). In 87 patients the clinical diagnosis of Down syndrome was confirmed cytogenetically. This high proportion of Down syndrome patients can be expected in a population of moderately, severely and profoundly mentally retarded patients. However, the proportion of mosaic trisomy 21 (n=11; 13%) was higher than expected (2.4%) and may be due to the fact that patients with a milder clinical phenotype, as seen in trisomy 21 mosaicism, reach an older age (for review see [43]). Structural autosomal abnormalities were diagnosed in 7 patients, including one patient with a partial trisomy 9p phenotype and 6 patients with well-known deletion syndromes. The patient with the rare complex chromosomal rearrangement was profoundly mentally retarded with macrocephaly but without minor anomalies. Sex chromosomal abnormalities included only numerical abnormalities. There was one patient with Klinefelter syndrome

Table 13.Overview of previous systematic etiological studies and the present study

Study	Number	Level MR	Unknown	Chromosomal (Down syndrome) (1)
Czeizel et al. [15]	1364	Mild/mod/ severe	172 (12.6%)	72 (5.3 %) (47 (3.4 %))
Thoene et al. [16]	727	Moderate/ severe	ND	72 (9.9%) (42 (5.8 %))
Fryns et al. [17]	173	Severe	20 (11.56%)	26 (15.1%) (22 (12.7%))
Dereymaeker et al. [18]	158	Mod/severe	29 (18.4%)	21 (13.3%) (14 (8.9%))
Fryns et al. [19]	262	Moderate	80 (30.5%)	46 (17.5%) (43 (16.4%))
Fryns et al. [20]	114 (52F)	Mod/severe	35 (30.7%)	26 (22.8%) (20 (17.5%))
Volcke et al. [21]	274 (0F)	Moderate	142 (51.8%)	9 (3.3%) (4 (1.5%))
Haspeslagh et al. [22]	307 (0F)	Severe	180 (58%)	23 (7.4%) (19 (6.2%))
Volcke et al. [23]	57 (44F)	Mild/borderline	31 (54.4%)	1 (1.8%) (0)
Farag et al. [24]	400	Severe (IQ<50)	40 (10%)	37 (9.25%) (34 (8.5%))
Temtamy et al. [25]	116	Borderline/mild/ severe	32 (27.6%)	4 (3.4%) (3(2.6%))
Schaap et al. [26]	116	Mod/severe	59 (50.9%)	11 (9.5%) (7 (6%))
Claes [27]	454 (166F)	Mild/mod	318 (84%)	21 (6%) (7 (1.5%))
Devriendt *et al.* [28]	66 (19F)	Mild/mod/ severe	32 (48.5%)	22 (33%) (19 (29%))
Félix et al. [29]	202	Severe/mild	70 (34.65%)	69 (34.2%) (65 (32.15%))
Lantigua-Cruz et al. [30]	512 (206F)	Severe	66 (12.9%)	213 (41.6%) (205 (40%))
Present study	471 (35F)	Mild to profound	233 (49.5%)	100 (21.2%) (87 (18.5%))

(1): Total number of patients with a chromosomal abnormality, including Down syndrome.
(): number of patients with Down syndrome.
(2): Number of patients with idiopathic MR and with a positive family history of non-specific MR.
(3): Number of patients with idiopathic MR and with family data compatible with X-linked MR.
F: number of females.

Monogenic disorders	MCA/MR	CNS	Acquired	(2)Unknown MR / nonspec fam MR	(3) Unknown MR / X-L fam MR
96 (7%)	-	-	396 (29%)	540 (39.6%)	ND
30 (4.1%)	ND	ND	ND	ND	ND
34 (19.5%)	7 (4%)	8 (4.6%)	75 (43.4%)	9 (5.2%)	-
36 (22.8%)	8 (5.1%)	6 (3.8%)	51 (32.3%)	7 (4.4%)	ND
44 (16.8%)	5 (1.9%)	4 (1.3%)	83 (31.7%)	24 (9.2%)	11 (4.2%)
21 (18.4%) 3 FRAXA	4 (3.5%)	1 (0.9%)	27 (23.7%)	18 (15.8%)	3 (2.6%)
44 (16%)	5 (1.8%)	9 (3.3%)	65 (23.7%)	22 (8%)	22 (8%)
43 (13.9%)	6 (1.9%)	-	57 (18.4%)	53 (17.3%)	13 (4.2%)
3 (5.3%)	-	-	23 (40.4%)	ND	6 (10.5%)
137 (34.25%)	22 (5.5%)	7 (1.75%)	175 (39.25%)	ND	ND
13 (11.2 %)	28 (24.1%)	15 (12.9%)	6 (5.2%)	ND	ND
16 (13.8%)	4 (3.4%)	-	26 (22.4%)	6 (5.2%)	3 (2.6%)
39 (10%)	-	-	-	46 (10.1%)	23 (5.1%)
4 (6%) 4 FRAXA	2 (3%)	3 (4.5%)	3 (4.5%)	5 (7.6%)	2 (3%)
25 (12.37%)	8 (3.96%)	8 (3.9%)	21 (10.39%)	8 (4%)	-
28 (5.5%)	ND	5 (0.9%)	200 (39%)	ND	ND
61 (13%)	-	8 (1.7%)	69 (14.6%)	38 (8%)	35 (7.4%)

Table 14. Overview of previous systematic cytogenetic studies and the present study

Study	Number	Mental level	Chromosomal (Down syndrome)	Remarks
Mounoud et al. [31]	82 (39F)	Mild/Profound	25 (30.5%) (18 (22%))	
Speed et al. [32]	2770 (1205F)	MR	297 (10.7%) (250 (9%))	
Sutherland, [33]	588 (258F)	Borderline/Profound	90 (15.3%) (73 (12.4%))	
Jacobs et al. [34]	475 (191F)	Borderline/Profound	57 (12%) (40 (8.4%))	
Ally and Grace, [35]	512 (136F)	MR	57 (11.1%) (42 (8.2%))	
Gripenberg et al. [36]	1062	MR	350 (33%) (305 (28.7%))	
Kondo et al. [37]	449 (188F)	Mild/Profound	37 (8.1%) (33 (7.3%))	
Nelson and Smart, [38]	720 (?F)	MR	148 (20.5%) (127 (17.6%))	
Brøndum-Nielsen et al. [39]	476 (227F)	Mild/Profound	76 (16%)) (58(12.2%))	2 (0.4%) FRAXA
Fryns et al. [40]	1991 (937F)	Moderate/Severe	423 (21.2%) (295 (14.8%))	57 (2.9%) FRAXA
Schreppers-Tijdink et al. [41]	1170 (449F)	Severe/Profound	258 (22.1%) (167 (14.3%))	21 (6.8%) FRAXA
English et al. [42]	512 (0F)	MR	110 (21.5%) (65 (12.7%))	30 (5.9%) FRAXA
Present study	471 (35F)	Mild to profound MR	100 (21.2%) (87 (18.5%))	16 (3.4%) FRAXA

F: number of females

(47,XXY) and one patient with 47,XYY syndrome. These figures are comparable to the incidence in the normal population and confirm that there is no relation with MR [44, 45]. The patient with 48,XXYY karyotype had mild dysmorphic features but no behavior problems. Borghgraef et al. [46] reported behavior problems in four 48,XXYY males including personality disturbances with psychotic reactions, chaotic behavior, and violent and impulsive reactions.

In only 8 patients (1.7%) central nervous system malformations were diagnosed. Previous studies also showed between 0.9% and 12.9% of CNS malformations (table 13). This can be explained by the small groups of patients who received brain imaging, because of the technical difficulties to perform brain-imaging.

Monogenic disorders were diagnosed in 61 patients (13%). In previous systematic surveys monogenic diagnoses were found in 4.1 to 34.25% and MCA/MR syndromes in 1.8% to 24.1% (table 13). The 5 patients (1.1 %) with microdeletion syndromes were classified in the group of chromosomal disorders. Comparison with previous studies on systematic etiological surveys is difficult, since other classification systems were used. The degree of MR in these populations was also variable and therefore not always comparable with the present population. Mental retardation has been well-documented in tuberosis sclerosis, Zimmermann-Laband syndrome, Steinert disease, Cornelia de Lange syndromes type 1 and type 2, Apert syndrome and Sturge-Weber syndrome. In Stickler syndrome and Waardenburg type 2 syndrome mental abnormality has been reported in individual patients [47, 48]. The patient with limb-mammary syndrome (LMS) (Pallister syndrome) was member of the large kindred with severe hand and foot anomalies and hypoplasia or aplasia of the mammary gland and nipples, and gene localization on 3q27 [49]. He was the only mentally retarded individual in this family. The LMS gene is probably the p63 gene that is involved in the EEC syndrome [50]. Mental retardation has been reported in the EEC syndrome [51-53]. The patient with the branchio-oto-renal syndrome (BOR) is candidate to perform microdeletion studies, since the responsible gene is thought to be located on chromosome 8q12.2-q21.2 [54]. Mental retardation in BOR can be explained by the extent of the microdeletion.

Autosomal recessive disorders were found in 25 patients. The patient with Fountain syndrome and the patient with Björnstad syndrome were reported elsewhere [55, 56]. Six patients presented with microcephalia vera without neurological symptoms. Diverse metabolic disorders were present in 16 patients. A metabolic disorders as the cause of MR was present in 10 patients (PKU (n=5), S-sulphocysteinuria (n=3), Sanfilippo syndrome, type A (n=1) and GM1-gangliosidosis type 3 (n=1)), and metabolic disorders not explaining the MR in 6 patients (Sly syndrome (n=1), Niemann-Pick syndrome, type B (n=1), cystinuria (n=1) and hyperprolinemia type 1 (n=3)) [57].

In 22 male patients the diagnosis of X-linked mental retardation was made (i.e. 5% of the male population). In 16 (72.7%) the diagnosis of fragile X syndrome was confirmed (i.e. 3.7% of the male population). These findings are in agreement with the general figures for fragile X syndrome in 2 to 6% of MR in males [58]. One of these patients had the Prader-Willi syndrome-like phenotype [59, 60]. Two patients presented X-linked mental retardation in association with marfanoid habitus (Lujan-Fryns syndrome MIM*309520) [61, 62]. In three brothers with nonspecific XLMR, a mutation in the ILRAPL1 gene, localized on Xp22.1-p21.3 was found

[13]. Stevenson [58] estimated that the fragile X syndrome may account for 30 to 40% of all XLMR and according to Claes [27] FRAXA accounts for 15% to 20% of the male XLMR patients. However, in the present population, more than 70% of the patients with XLMR have the fragile X syndrome. This finding is not surprising, as in more than 60% of males with XLMR clinical findings are nonspecific [58]. Also in the present study, a number of males with XLMR was not recognized on the basis of the clinical phenotype only. In the group of 233 patients with idiopathic type of MR, further family data were collected and showed familial MR with affected first and/or second degree relatives in 73 patients (69 males and 4 females). Among these 69 affected males there were 35 males with pedigree data compatible with XLMR, including 3 affected male sib pairs, with a distinct neurological syndrome of complicated spastic paresis in 1 of them. XLMR was thus considered in 57 of the 471 patients (i.e. 12.1% of the total population, and 24.1% of the males with idiopathic MR), including 16 fragile X males, 2 males with MRXS, 3 brothers with a mutation in the ILRAPL1 gene, 1 patient member of the MRX-44 family and 35 other males with nonspecific XLMR.

In the group of 233 patients with idiopathic MR additional parameters were analyzed: the occurrence of minor anomalies and neurological symptoms and biometric data on head circumference versus testicular volumes in males.

Minor anomalies were present in 41 (17.6%) patients. This percentage is lower than that found by Claes [27] in another MR population (27%). In patients with minor anomalies, the degree of MR was significantly more severe than in patients without minor anomalies. Cutis verticis gyrata was present in 3 severely to profoundly mentally retarded patients. A cutis verticis gyrata and mental deficiency syndrome (MIM 219300) was described by Åkesson [63, 64] in 47 mentally retarded patients in Sweden as a possible autosomal recessive inheritance condition.

Neurological abnormalities were noted in a large number of patients. Seizures were present in one third of the patients. The presence of epileptic was statistically significantly correlated with more severe MR. In 6 males with familial mental retardation, spastic paraplegia was present. Mutation analyses are planned as the genes for complicated spastic paraplegia 1 (MASA spectrum; L1CAM; L1 cell adhesion molecule; Xq28) and complicated spastic paraplegia 2 (Pelizaeus-Merbacher syndrome; PLP; proteolipid protein; Xq21.1) have been cloned.

In the 215 males the combination of microcephaly and micro-orchidism was higher than expected; however, no statistically significant correlation was found. Macrocephaly and micro-orchidism were present in only one male. The combination of macrocephaly and macro-orchidism was present in 5 males (2.3%)

and this finding was statistically significant. Since we were only interested in the combination of microcephaly and micro-orchidism and in the combination macrocephaly and macro-orchidism, only these 2 correlation tests were performed. Even after multiplying the P-value (Fisher exact test) by 2 (two correlation tests), the combination of macrocephaly and macro-orchidism remained statistically significant. Two of these patients with macrocephaly-macro-orchidism also had minor anomalies and 2 had behavior problems. The study of Claes [27], showed macrocephaly with macro-orchidism in 3% of the males. Since several XLMR syndromes are described which present with the combination of micro- and macro-orchidism and micro- or macrocephaly further investigations, such as looking for point mutations in the FMR-1 gene, are necessary in these groups of MR patients [58, 65].

In the group of 18 females 3 (16.7%) had microcephaly. One mildly mentally retarded microcephalic female also had mild neurological abnormalities.

Before systematic evaluation, only 21.8% (103/471) of the patients had a known diagnosis. After this survey, 50.5% (238/471) of the investigated patients had a definite diagnosis. However, the cause and the etiology of the MR could not always be explained by the presence of a diagnosis [57]. The global percentage of the diagnoses was also biased in this institution since a large number of persons with the clinical diagnosis of Down syndrome was cytogenetically confirmed (n=87).

The present study agrees with the recommendations of the American College of Medical Genetics concerning the evaluation of mental retardation [66]. The individual, his family and caregivers do benefit from a focused clinical and laboratory evaluation. Therefore, the evaluation should be complete and include anamnestic data concerning early childhood, physical and neurological examination and assessment of the behavioral phenotype. Technical investigations should include chromosomal studies, accompanied by molecular DNA studies for the Fragile X syndrome (expansion of the CGG repeat in the FMR-1 gene). Metabolic testing and neuro-imaging should be reserved for selected groups of patients [66]. Longitudinal evaluation may be important to find the diagnosis, and for delineation of the physical and behavioral phenotype [66]. Systematic studies of diagnoses in an older population of mentally retarded patients are helpful in recognition and prevention of medical complications. In contrast to persons without MR, persons with severe MR do have 2.7 times, and persons with mild MR 2.2 times more comorbidity. The estimated rates of visual and hearing problems for people with intellectual disability are much higher than in people without MR [67-70]. In the group of patients with Down syndrome these medical complications are well known [43, 70]. In sporadic syndromes, scarce reports on medical complications at an older

age are found in the literature. Therefore, this study is also a first step towards future studies concerning medical complications in older patients.

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Part 2

Ageing in mental retardation: a biomedical approach

Content Part 2

CHAPTER 1
CHROMOSOMAL SYNDROMES

Content Chapter 1

1.1 DOWN SYNDROME

1.1.1 DOWN SYNDROME IN A POPULATION OF ELDERLY MENTALLY RETARDED PATIENTS: GENETIC-DIAGNOSTIC SURVEY AND IMPLICATIONS FOR MEDICAL CARE

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ABSTRACT

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 confirm the clinical diagnosis and are essential for genetic counseling purposes.

INTRODUCTION

Down syndrome (DS) is the most frequently identified cause of mental retardation with an incidence of 1/700 to 1/1000 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% of the patients 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 ageing 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 9 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 2-22 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 Ageing 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 already 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 mobility 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^3, the middle ear pressure (MEP), at or near the 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^3.

Thyroid functioning

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 patients were diagnosed with epilepsy.

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	50-59yrs	≥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%)

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.

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)	

Mental functioning

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 had a mosaic pattern of double aneuploidy (Down-Turner patient) (Table II).

TABLE III. Relation level of mental retardation and karyotype

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

MR: mental retardation

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.

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

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

TABLE V. Results of vision tested in 92 patients

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

+C: with correction; -C: without correction

TABLE VI. Classification of the population Down syndrome patients according to age and loss of visual acuity

Visual acuity	Age					
	≤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%)
≤ 0.30	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%)

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 loss. No statistically significant correlation was found between the severity of mental retardation and loss of visual acuity (Chi-square in contingency table (2x3); P = 0.08; 2 degrees of freedom).

TABLE VII. Relation level of mental retardation and loss of visual acuity

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 %)

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 patients 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 the 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 VIII. Classification of the population Down syndrome patients according to age and hearing loss

Hearing loss	Age					
	≤29 yrs	30-39 yrs	40-49yrs	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%)

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 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.

TABLE X. Severity of hearing loss in relation to the type of hearing loss and according to age (in years)

Hearing loss	<29 yrs			30-39 yrs			40-49 yrs			50-59 yrs			>60 yrs	Total
	M	P	C	M	P	C	M	P	C	M	P	C	M	
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 1 patient of 43 years with a moderate hearing loss

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 patients 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 (2x3); P = 0.17; 2 degrees of freedom).

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

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, 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 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 functioning

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 (2x3); $P = 0.8$; 2 degrees of freedom).

During this study, ten patients died, seven had dementia, and six were in the age group of 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 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 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 to 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 the visual problems and the 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 [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 two 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 at 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 determine 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 of 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 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 ten 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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1.1.2 DOWN-TURNER SYNDROME: CASE REPORT AND REVIEW

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ABSTRACT

We present a male patient with Down-Turner mosaicism (45,X/46,X,+21/47,XY,+21) and review 27 similar cases reported so far. Clinical features of Down syndrome were present in all cases, whereas a combination of features of both Ullrich-Turner syndrome and Down syndrome was reported in 61% of the patients. However, one has to bear in mind that several stigmata of Ullrich-Turner syndrome can also be present in patients with Down syndrome and vice versa.

In most of the patients two different cell lines were encountered, although cases with one, three and even four different cell lines have been reported. Of 28 patients, 21 showed female external genitalia, four were phenotypically male, and three showed ambiguous genitalia. Only 6 patients (21%) carried a Y chromosome, which is far less than expected.

INTRODUCTION

Chromosomal aneuploidy is quite frequent and may involve autosomes, as in Down syndrome, or sex chromosomes, as in Ullrich-Turner syndrome. In contrast, double aneuploidy involving both autosomal and sex chromosomes is very rare. Sex chromosomal aneuploidy in combination with trisomy 21 includes Down-Klinefelter, Down-XXX, Down-XYY, and Down-Turner syndrome (1-4). Of these, Down-Turner syndrome is one of the most rare with only 27 cases being reported so far. We present a new case of Down-Turner mosaicism (45,X/46,X,+21/47,XY,+21), which was found during routine screening of a 59 year old male to confirm the clinical diagnosis of Down syndrome and to rule out an inherited translocation. Cytogenetic and clinical features of all known cases are reviewed.

CASE REPORT

A 59 year old male, institutionalized from the age of 8 years, was presented for cytogenetic analysis to confirm the clinical diagnosis of Down syndrome and to rule out the presence of an inherited chromosome aberration. The proband was the fourth child of non-consanguineous parents. There had been one miscarriage between the first and second children. At birth both parents were 40 years old. There was no family history of either Down or Turner syndrome. When the proband was 7 months old, psychomotor retardation was noticed. He walked at the age of 2 years 6 months and developed speech at 5 years. At the age of 7, he weighed 20.7 kg (25th centile) with a height of 117 cm (25th centile), and features of Down syndrome were first noticed then. Clinical neurological investigation at the age of 32 was normal, but a pneumoencephalogram showed periventricular atrophy. Substitution therapy was started for primary hypothyroidism, when he was 49 years old. On the Vineland Adaptive Behavior Scale his total psychological score was 4 years 8 months at the age of 53. However, he was able to write and read. A few years later a moderate bilateral perception hearing loss was diagnosed, with a loss of 35 dB on the left and 53 dB on the right (Fletcher Index). He has recently developed diabetes mellitus type II which was treated orally.

Recent investigation showed a well nourished, short statured male with a height of 156 cm (<3rd centile) and a weight of 64.5 kg (50th centile). He had a brachycephalic skull with a head circumference of 52.3 cm (<3rd centile). His hair was sparse and there was a low posterior hairline. He had a round face with small, upward slanting palpebral fissures, a flat midface, and a normal tongue. His ears were asymmetrical and measured 7 cm on the right and 7.2 cm (75th to 97th centile) on the left (Fig. 1). His neck was short and broad and the thorax wide with an internipple distance of 22 cm (97th centile). Heart auscultation was normal and he had normal sized testes. The hands were broad, with a total hand length of 17 cm (25th centile) bilaterally, the fifth fingers were normal, and there were no simian creases. The foot length was 21 cm (<3rd centile) bilaterally, there was partial syndactyly of the second and third right toe, and there was no sandal gap.

Cytogenetic studies

Chromosome analysis was performed according to routine procedures. During analysis of 15 GTG banded metaphases derived from cultured peripheral lymphocytes, two different cell lines were found. Therefore, the study was extended to a total of 100 mitoses. This analysis showed a mosaic pattern of double

Figure 1. Facies and profile of the patient.

aneuploidy : 45,X/46,X,+21/47,XY,+21 (79/2/19). Subsequently, a skin biopsy was obtained from the right upper limb. Chromosome analysis of 50 cultured fibroblast cells after routine GTG banding also showed a mosaic pattern, but different from the lymphocytes in that the 46,X,+21 cell line was not found: 45,X/47,XY,+21 (36/14).

Discussion

Double aneuploidies involving both a sex chromosome and an autosome appear to be quite rare, with Down-Turner syndrome being among the most rarely reported. In the analysis of our patient we encountered several specific features of Down syndrome (mental retardation, brachycephaly, upward slanting palpebral fissures, a flat midface, and short stature) as well as Ullrich-Turner syndrome (short and broad neck, low posterior hairline, wide thorax with a large internipple distance, and short stature). Mental retardation was mild as he was able to write and read and he was quite old for a pure trisomy 21 patient. There were no signs of dementia. Cytogenetic studies proved that this was because of a mosaic chromosomal pattern with trisomy 21 in only a minority of cells in two different tissues. The patient was phenotypically male although chromosome analysis showed a Y chromosome in only 19% and 28% of cultured peripheral lymphocytes and fibroblast cells, respectively.

Review of the literature

A total of 34 cases of Down-Turner syndrome have been reported so far. However, three of these cases apparently were diagnosed purely on clinical features without any cytogenetic confirmation (5, 6). Since we reviewed only karyotyped cases, these three were not included in the table and will not be considered further. Another three cases of Down-Turner mosaicism in which one of the X chromosomes showed a deletion were not included either, as they represent a different genetic entity: 47,XX,+21/47,XX,p-q-,+21; 47,X,del(X)(p11),+21, and 47,X,Xq-,+21 (7-9). Lastly, a complex case of trisomy 21 associated with XO/XX/XXX, was also excluded (10).

The clinical features and chromosomal patterns of the remaining 28 patients, including our own case, are summarized in table 1.

Features of Down syndrome against Ullrich-Turner syndrome

Eleven of the 28 patients (39%) had the typical phenotype of pure Down syndrome, including short stature, flat face, oblique palpebral fissures, depressed nasal bridge, Brushfield spots, large, protruding tongue, small ears, brachycephaly, short broad hands and feet, short fifth fingers, a space between the first and second toes, and hypotonia at birth (cases 1, 4, 5, 7, 8, 10, 12, 13, 14, 22 and 23). Four patients (14%) showed clear features of both Down and Turner syndromes (cases 3, 15, 20 and 21), while in 12 patients (43%) clear signs of Down syndrome and only milder features of Ullrich-Turner syndrome were reported (cases 2, 6, 9, 11, 16, 17, 18, 19, 24, 25, 27 and 28). These less distinct features of Ullrich-Turner syndrome included: oedema of the hands and feet at birth, delayed sexual development, short stature, webbing of the neck, and ambiguous genitalia. In three of the 12 cases (cases 6,9 and 17) oedema of the hands and feet was reported and in two patients (cases 24 and 28) delayed sexual development was noted. Both features are quite specific for Ullrich-Turner syndrome, whereas the other signs may be present in Down syndrome as well. Therefore, the remaining seven patients could also be regarded as typical Down syndrome patients based on the published data. However, since all 12 patients were earlier described as showing signs of both Down and Ullrich-Turner syndromes we included them is this group.

In one patient only mild stigmata of both Down and Ullrich-Turner syndrome were described (case 26).

Not a single patient has been reported with a pure Ullrich-Turner phenotype as characterized by a short stature, delayed sexual development, low posterior hairline, shield chest, multiple pigmented naevi, cubitus valgus and webbing of the neck.

Table 1. Down Turner syndrome: Clinical features and cytogenetic findings in cultured peripheral lymphocytes of all 28 reported cases including the present one

Case	Reference	Chromosome Pattern
1	Baguena Candela 1966 (15)	46,X,+G
2	Townes et al.1975 (2)	45,X/46,X,+21
3	Taylor et al.1970 (16)	45,X/47,XX,+G *
4	Cohen & Davidson 1971 (1)	45,X/47,XX,+21 *
5	Barakat&DerKaloustian1973 (17)	45,X/47,XX,+G
6	Hustinx et al.1974 (18)	45,X/47,XX,+21 *
7	Jansen et al.1991 (4)	45,X/47,XX,+21
8	Prieur et al.1972 (19)	45,X/47,XY,+21 *
9	Hustinx et al.1974 (18)	45,X/47,XY,+21
10	Baguena Candela 1965 (20)	46,X,+G/46,XX
11	Medenis et al. 1962 (21)	46,X,+G/47,XX,+G
12	Root et al. 1964 (22)	46,X,+21/47,XX,+21
13	Van Wijck et al.1964 (23)	46,X,+21/47,XX,+21
14	Pfeiffer et al.1968 (24)	46,X,+21/47,XX,+21
15	Gatrad 1981 (3)	46,X,+21/47,XX,+21
16	MacFaul et al.1981 (25)	46,X,+21/47,XX,+21
17	MacFaul et al.1981 (25)	46,X,+21/47,X,i(Xq),+21
18	Santos Mello et al.1974 (26)	46,X,+21/47,XY,+21
19	Yeung&Yang 1976 (12)	46,X,+21/47,XY,+21
20	Villaverde&Da Silva1975 (27)	45,X/46,X,+G/47,XX,+G *
21	Present report 1994	45,X/46,X,+21/47,XY,+21 *
22	Grosse et al. 1971 (28)	45,X/46,XX/47,XX,+G
23	Edgren et al. 1966 (29)	45,X/46,XY/47,XY,+21 *
24	van Gelderen et al.1967 (30)	46,X,+G/46,XX/47,XX,+G
25	Singh et al. 1975 (11)	46,X,+G/46,XX/47,XX,+G
26	Feiertag-Koppen et al1966 (31)	45,X/46,X,+G/46,XX/47,XX,+G
27	Singh et al. 1975 (11)	45,X/46,X,+G/46,XX/47,XX,+G
28	Singh et al. 1975 (11)	45,X/46,X,+G/46,XX/47,XX,+G

* Cases in which a fibroblast culture also was cytogenetically analyzed:

- Cases 3,8 and 23: fibroblast cells = peripheral lymphocytes
- Cases 4 and 6: fibroblast cells: 47,XX,+21
- Case 21 (present report): fibroblast cells: 45,X/47,XY,+21
- Case 20: the cytogenetic findings of the cultured fibroblast cells are shown. The 47,XX,+G cell line was not found in the peripheral lymphocytes (45,X/46,X,+G)

Genitalia	Clinical Appearance	Age of Patient	Parental Age	
			Mother	Father
F	DOWN	-	-	-
F	DOWN + turner	8y	29	-
F	DOWN + TURNER	15y	-	-
F	DOWN	6 months	-	-
F	DOWN	newborn	36	40
F	DOWN + turner	9.5y	30	37
F	DOWN	8y	24	26
M	DOWN	5y	-	-
M	DOWN + turner	15y	30	37
F	DOWN	-	-	-
F	DOWN + turner	9y	-	-
F	DOWN	2 months	42	44
F	DOWN	3 months	26	28
F	DOWN	9y	-	-
F	DOWN + TURNER	5y	26	28
F	DOWN + turner	newborn	36	65
F	DOWN + turner	newborn	38	-
A	DOWN + turner	-	18	-
A	DOWN + turner	5 months	36	40
A	DOWN + TURNER	25y	35	-
M	DOWN + TURNER	59y	40	40
F	DOWN	7y	27	28
M	DOWN	25y	32	28
F	DOWN + turner	21y	37	-
F	DOWN + turner	16.5y	33	-
F	down + turner	16y	27	29
F	DOWN + turner	17.5y	31	33
F	DOWN + turner	13y	33.5	31

F: female; M: male; A: ambiguous genitalia; DOWN: obvious features of Down syndrome; down: mild features of Down syndrome; TURNER: obvious features of Turner syndrome; turner: mild features of Turner syndrome

Thus, clinical features of Down syndrome were always present, while a combination of Ullrich-Turner and Down syndrome features were found in 17 patients (61%). Apparently, phenotypic effects of even a relatively low percentage of trisomy 21 cells are much more prominent than those of the monosomy X cells. However, the proportion of trisomy 21 versus monosomy X cells does not always correlate with the phenotype, which can probably be explained by a different mosaic distribution in various somatic tissues (11). This implies that the clinical diagnosis of Down-Turner syndrome based merely on the phenotype is very difficult to make and should be supported by cytogenetic studies in virtually all cases.

The fact that clinical features of two syndromes may coexist shows the relative autonomy of these chromosomes in morphogenesis (3, 12).

Chromosomal mosaicism in Down-Turner syndrome

Only one patient with Down-Turner syndrome has been reported who showed a single cell type (case 1) and is, therefore, not a true mosaic. All other cases are a combination of two (cases 2-19), three (cases 20-25), or even four cell lines (cases 26-28). Our patient (case 21) had three cell lines in cultured T lymphocytes, but only two in a fibroblast culture of a skin biopsy. However, since 46,X,+21 cells were found at a very low frequency in lymphocytes, we could easily have missed it if these cells had been present at a low frequency in the cells of the skin too.

Karyotype and gender

Only four of the 6 patients with a Y chromosome were phenotypically male while the other two showed ambiguous genitalia. One of these two patients had a bifid scrotum and a penoscrotal hypospadias with a urogenital sinus. A uterus and bilateral testes were present (case 18). The second patient also had a bifid scrotum, a perineal hypospadias and a urogenital sinus. He had bilateral small testes but no internal female organs (case 19). Of the 22 patients without a Y chromosome, 21 were phenotypically female. The remaining patient showed ambiguous genitalia, presenting with "hermaphroditic" external genitalia, a rudimentary uterus, and no ovaries or testes (case 20). This is in accordance with the observation that patients with an Ullrich-Turner mosaicism are known to show a wide spectrum of different phenotypic expression ranging from normal females, females with mixed gonadal dysgenesis and male pseudohermaphroditism to almost normal males (13, 14).

Our patient was phenotypically male although chromosome analysis showed a Y chromosome in only a minority of his cells. In general, the phenotypic appearance of the genitalia is probably a result of the chromosomal mosaicism as

present in the various tissues, since two patients who carried a Y chromosome and one with an X chromosomal mosaicism had ambiguous external genitalia.

Little mosaicism of Y chromosome in Down-Turner syndrome

From the 28 reported patients, only six (21%) had a Y chromosome, which is far less than expected. Since all described cases with Down-Turner syndrome showed clinical signs of Down syndrome, it seems unlikely that (male) patients with a Y chromosome in a certain proportion of their cells would not be traced. Assuming that the sex chromosomal mosaicism in the reviewed cases is probably caused by anaphase lagging, in XX zygotes loss of either X chromosome would be viable leading to a mosaic situation. However, in an XY zygote lagging of the Y chromosome only would lead to a mosaic fetus (45,X/46,XY), because lagging of the X results in a non-viable 45,Y cell. This effect considerably reduces the number of sex chromosome mosaics carrying a Y chromosome. Whether there are any other selection mechanisms reducing the number of Y chromosome mosaics in Down-Turner syndrome, for instance during embryogenesis, is unknown at present.

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1.2 DESCRIPTION OF PATIENTS WITH OTHER CHROMOSOMAL DISORDERS

1.2.1 CRI DU CHAT SYNDROME: THE CHANGING PHENOTYPE IN OLDER PATIENTS

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ABSTRACT

The cri du chat syndrome or 5p deletion syndrome is a well-delineated clinical entity and has an incidence of 1/50,000 in newborn infants. A de novo deletion is present in 85% of the patients. Ten to 15% are familial cases with more than 90% due to a parental translocation and 5% due to an inversion of chromosome 5. Although the size of the deleted segment varies, the critical segment that is deleted in all patients appears to be 5p15.2. The clinical picture is well known in younger patients and includes the typical high-pitched cry, psychomotor retardation, microcephaly, growth rate failure, and craniofacial abnormalities including round face, hypertelorism, broad nasal bridge, downward slanting palpebral fissures, and micrognathia. With advancing age, the clinical picture becomes less striking. We present seven patients with 5p deletion syndrome, who were between age 16 and 47 years. Comparing their phenotype at several ages, a change of their phenotype was noted. Some of the clinical characteristics became more evident such as long face, macrostomia, and scoliosis. All patients were severely or profoundly mentally retarded except one patient who was mildly mentally retarded. The diagnosis was difficult to make in some of the patients who were first seen at an older age. In some of them, the craniofacial appearance resembled that seen in Angelman syndrome. Most patients had periods of destructive behavior, self mutilation and aggression. The clinical diagnosis should be confirmed as soon as possible with cytogenetic investigation to provide specific support, prevention, and treatment of complications. Therefore, it is important to perform follow-up studies in young children to determine their outcome after infant-stimulation programs.

INTRODUCTION

The cri du chat syndrome, a chromosomal disorder characterized by a partial terminal or interstitial deletion of the short arm of chromosome 5, was first described by Lejeune et al. [1963]. About 85% of the patients have a de novo deletion. In 10- 15% there is a familial cause with a parental translocation in more than 90% and a familial para- or pericentric inversion of chromosome 5 in 5% [Chernos et al., 1992; Goodart et al., 1996; Kushnik et al., 1984]. Over 80% of the deletions are of paternal origin [Overhauser et al., 1990]. Niebuhr [1978a] showed that the typical clinical findings of the cri du chat syndrome were present when there was a deletion of the midportion of the 5p15 segment. Although the size of the critical segment varies, the critical segment that is deleted in all patients appears to be 5p15.2 [Niebuhr, 1978b; Chernos et al., 1992; Overhauser et al., 1994].

The incidence of the cri du chat syndrome was estimated as 1 in 50,000 newborn infants [Niebuhr, 1978a]. There is a male to female ratio of 0.73 [Niebuhr, 1978b; Oosterwijk et al., 1987; Wilkins et al., 1983].

Niebuhr [1978a] published an extensive review on epidemiological, cytogenetic, and clinical aspects in 331 patients with the cri du chat syndrome. The craniofacial anomalies included microcephaly, round face, downward slanting palpebral fissures, broad nasal bridge, cat-like cry, hypotonia, and mental deficiency. Although lack of speech was considered a characteristic of the syndrome, it is not yet known whether language comprehension is impaired to the same extent as language production [Cornish and Munir, 1998]. With advancing age the clinical picture becomes less striking, and the clinical diagnosis is difficult to make. With age the face lengthens and becomes "coarse" with prominent supra-orbital ridges, deep-set eyes, hypoplastic nasal bridge, and severe dental malocclusion, relatively large mouth, and full lower lip [O'Brien and Yule, 1995].

In the present study, seven patients were studied to further delineate the natural course of this syndrome (Table I) (Figs. 1-7).

CLINICAL REPORTS

Patient 1

The patient (Fig. 1), a 47-year-old man, institutionalized since age 10 years, is profoundly mentally retarded. He was the first child of healthy nonconsanguineous parents. His father suffered from progressive hearing loss. The mother, two younger sisters and brother were healthy. Pregnancy was uneventful. He was born at 36

Figure 1
Patient 1: Microcephaly, the round face and broad nasal bridge become longer and coarse in adulthood

weeks of gestation. Birth was difficult, and there was asphyxia. Birth weight was 1,500 g (< 3rd centile). There were feeding difficulties, and he had a weak cry. A few months after birth he developed seizures. When he was age 3 months, he underwent a bilateral mastoidectomy. Psychomotor development was severely delayed. He could sit at age 3 years but never learned to walk or to speak. Clinical investigation at age 10 years showed a small boy with a length of 114 cm (< 3rd centile), weight of 18 kg (< 3rd centile) and head circumference (OFC) of 44.5 cm (< 3rd centile). Thorax was barrel-shaped and asymmetric. There was spasticity of the lower limbs and scoliosis. At age 21 years there was microcephaly, small stature, asymmetric thorax and kyphoscoliosis and spastic and atrophic limbs with contractures in the knee-joints. He was afraid of noises. At age 32 years, he suffered from stomach ulcers and was treated with omeprazole. Periodic behavior problems, caused by negative stimuli, included self mutilation, head banging, and destroying

Table I. Overview of the Manifestations of the Patients

	Case 1 (male)	**Case 2 (female)**	**Case 3 (male)**
Age	47 years	45 years	44 years
Cytogenetics	del(5)(p14.1)	del(5)(p13.3)	del(5)(p13.3)
History			
Birth weight (g)	1,500	2,500	< 3,000
Feeding difficulties	+	+	+
Cat-like cry	+	+	ND
Convulsions	+	-	-
Mental retardation	profound	severe	profound
Speech development	noises	a few words	a few words
Voice	male	high-pitched	hoarse, male
Neurology	spasticity	broad-based clumsy gait	ataxia-like broad-based gait
Childhood behavior	automutilation	automutilation destroys own things head banging scratching	automutilation
Adult behavior	automutilaton destroys own things afraid of noises laughing	disobeys teases sweet afraid of noises nail biting hyperactive	handbiting jumping hyperactive hand-flapping
Dysmorphism			
Microcephaly	+ (48 cm) brachycephaly	+ (48.8 cm) brachycephaly	+ (51 cm)
Face shape	round-long	round-long asymmetry	long-coarse-old aspect asymmetry
Hair	premature gray	premature gray soft	premature gray
Eyes	divergent strabismus	divergent stabismus myopia (bilateral)	normal
Palpebral fissures	upward	normal	normal
Hypertelorism	-	+	+
Epicanthus	-	+	+ (R)
Nose	coarse asymmetric	coarse hook-shaped	bulbous tip
Maxilla hypoplasia	+	+	+
Mouth	macrostomia macroglossia thin lips	dental maloccusion	macrostomia prognathia thin lips
Ears	simple	simple	thick helices
Extremities	large hands clinodactyly V	short matacarpals and metatarsals	short metacarpals
Palmar creases	-	variant simian creases	bilateral simian creases
Scoliosis	severe	mild	-

R = right; ND = no data

Case 4 (male)	**Case 5 (female)**	**Case 6 (male)**	**Case 7 (female)**
43 years	25 years	16 years	18 years
del(5)(p13.3)	del(5)(p13.3)	del(5)(p13.3)	del(5)(p15.31)
ND	3,350	3,100	2,050
ND	+	+	+
ND	+	+	+
-	+	-	-
severe	severe	severe	mild
a few words	a few words	a few words	normal
male	high pitched	high pitched	high pitched
normal	spasticity	ataxia-like	normal
	(post operative complications)	broad-based gait	
aggressive	automutilation	automutilation	nervous
	picking	trichotillomania	
	biting	cruel to others	
	scratching	head banging	
automutilation	demands attention	teases	nail biting
aggressive	teases		impulsive
destructive			disobeys
screams			
teases			
+ (50.8 cm)	+ (50.5 cm)	+ (50.2 cm)	- (54 cm)
brachycephaly			
long-coarse	long	long	round-long
	asymmetry	asymmetry	asymmetry
premature gray	premature gray	normal	normal
divergent strabismus	normal	normal	normal
normal	normal	normal	normal
+ (mild)	normal	+	-
+ (R)	+	+	+
coarse	coarse	high nasal bridge	large (profile)
+	+	+	+
macrostomia	macrostomia	macrostomia	macrostomia
dental malocclusion	dental malocclusion	thin lips	high palate
caries, full lips	thin lips		retrognathia
thick helices	ear pit R	normal	normal
short metacarpals	clinodactyly V	clinodactyly V	short IV/V
clinodactyly V			metacarpals
flat feet			flat feet
bilateral simian	-	bilateral simian	siman crease R
creases		creases	
-	severe	severe	-

his own cloths.

Present investigation showed a profoundly mentally retarded male with small stature, weight of 48 kg (8 kg < 3rd centile), OFC of 48 cm (5 cm < 3rd centile), brachycephaly, gray hair, small forehead, upward slanting palpebral fissures, flat midface, short philtrum, macrostomia, large tongue, thin lips and simply formed ears. Thorax was barrel-shaped and there was severe kyphoscoliosis. Testes were small. Hands were large with clinodactyly of the fifth fingers. He was not ambulatory due to spasticity of lower limbs with contractures. There were clubfeet, and the toes were irregularly positioned with a longer fifth toe. Although contact was good, there was no speech and he made only sounds. Results of screening for inborn errors of metabolism were negative. Chromosomal analysis on peripheral blood lymphocytes showed a male karyotype with a terminal deletion of the short arm of chromosome 5. His karyogram was 46,XY,del (5)(p14.1). Cytogenetic status of his mother was normal. Cytogenetic studies of his father were not possible.

Patient 2

Figure 2
Patient 2: Coarsing of the typical cri du chat facies in childhood

The patient (Fig. 2) was a 45-year-old severely mentally retarded woman. She was the second child of nonconsanguineous parents. Her father was age 37 years and her mother age 24 years at the time of her birth. Pregnancy was uneventful. She was born at 37 weeks of gestation. Birth weight was 2,500 g (25th-50th centile). Cry was high pitched. There were neonatal feeding problems. Psychomotor development was retarded. She could walk at age 6 years. Periodic behavior problems were present and included self mutilation, destroying her own cloths, head

banging, and scratching. Clinical investigation at age 30 years showed severe microcephaly, divergent strabismus, hypertelorism, epicanthus, bilateral severe myopia, hook-shaped nose, simple ears, and normal hearing. The thorax was asymmetric, and kyphoscoliosis was present. X-ray studies showed short metacarpal and metatarsal bones. Her motor development was mildly delayed, and she could speak a few words. An electroencephalogram was normal and cerebral computed tomography-scan showed dilatation of the lateral ventricles and widened basal cisternae. An X-ray film of the back showed scoliosis and lumbar ribs.

Present investigation showed a severely mentally retarded female with a length of 148.5 cm (2.5 cm < 3rd centile), an OFC of 48.8 cm (3.2 cm < 3rd centile), round face, soft and premature gray hair, flat midface, hypertelorism, epicanthal folds, severe myopia, "coarse" nose, simple ears, dental malocclusion, and short philtrum. The neck was short. She had mild kyphoscoliosis and bilateral flatfeet. Walking was broad-based. Contact was good; she could speak a few words with a high pitched voice. Cytogenetic investigation of peripheral blood lymphocytes showed a female karyotype with a deletion of the distal part of chromosome 5. Her karyotype was 46,XX,del(5)(p13.3). Cytogenetic studies of her parents were not possible since they died before the diagnosis was made in their daughter. Cytogenetic findings of her sister were normal.

Patient 3

Figure 3
Patient 3: Note the long coarse face and premature gray hair

The patient (Fig. 3), a 44-year-old profoundly mentally retarded man, was the youngest of two children of healthy nonconsanguineous parents. His older sister

was healthy. Birth weight was below 3,000 g. There were neonatal feeding problems with swallowing difficulties. He had no epileptic attacks.

Present examination showed a profoundly mentally retarded male with weight of 60 kg (25th centile), OFC of 51 cm (2 cm < 3rd centile), long "coarse" face, facial asymmetry, flat maxilla, prognathism, gray hair, normal eyes, nose and ears. There were bilateral simian creases present, and the metacarpals were slightly short. Neurological examination showed ataxia, and walking was broad-based. He produced a few words with a hoarse voice. His behavior was specific with jumping and waving of the hands when he was happy and handbiting when he was frustrated. His karyotype was 46,XY,del(5)(p13.3). Cytogenetic studies of his parents could not be performed because they died before the chromosomal diagnosis was confirmed in their son. Cytogenetic findings of his sister were normal.

Patient 4

Figure 4
Patient 4: Note the long face, full lips and open mouth

The patient (Fig. 4), a 43-year-old severely mentally retarded man was the second child of healthy nonconsanguineous parents. His four sibs were normal. Medical history showed minimal speech development. There was no epilepsy. He had often aggressive periods.

Present examination showed a severely mentally retarded male with length of 170 cm (25th centile), weight of 70 kg (25th centile), OFC of 50.8 cm (2.2 cm < 3rd centile), long "coarse" face, flattened occiput, prematurely gray hair, epicanthus on the right side, divergent strabismus, thick helices of ears, broad nasal bridge, flat

maxilla, open mouth, and full lips. Several teeth were extracted. There was hyperpigmentation of his face and left upper limb. The second finger of his left hand was amputated after an accident. A simian crease was present bilaterally. The neck was short and the thorax was slightly barrel-shaped. Aggressive periods were present with yelling, beating, and destructive behavior. Although he could speak some words, he produced mostly sounds. His karyotype was 46,XY,del(5)(p13.3). Cytogenetic studies of his parents could not be performed.

Patient 5

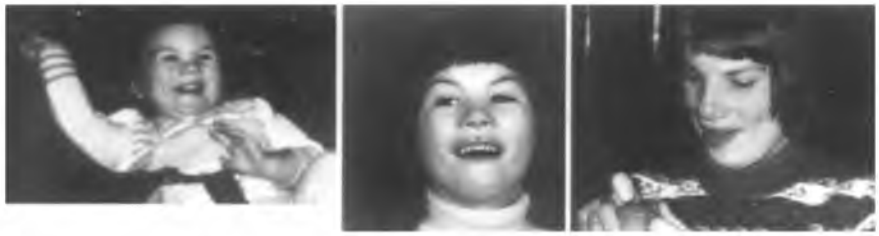

Figure 5
Patient 5: With advancing age the phenotype becomes less typical

This 25-year-old woman (Fig. 5) was the second child of healthy nonconsanguineous parents. Her older brother was normal. Pregnancy and birth were uncomplicated. Birth weight was 3,350 g and length 50 cm. Cry was high pitched. She could walk at age 5 years. She suffered from febrile convulsions. She developed very severe scoliosis and was treated surgically at age 18 years. However, a severe postoperative complication lead to spasticity of the lower limbs. Present examination showed a 25-year-old severely mentally retarded, non-ambulant woman. Stature was normal, weight was 60 kg (50th-75th centile) and OFC 50.5 cm (1.5 cm < 3rd centile). She had a long, mildly asymmetric face, flat midface, epicanthal folds, ear pit on the right side, coarse nose, deep philtrum, large mouth, dental malocclusion, and thin lips. Her hair was prematurely gray. The neck was short and there was bilateral clinodactyly of the fifth fingers. Language comprehension was much better than language production. Her voice was high pitched. There were difficulties with breathing and swallowing. Although

improving with advancing age, she had periodic behavior problems of self mutilation, biting and scratching. Karyotype was 46,XX,del(5)(p13.3), de novo.

Patient 6

Figure 6
Patient 6: Microcephaly and broad nasal bridge. At older age the face becomes longer

This boy (Fig. 6) was the second child of healthy nonconsanguineous parents. His older sister was healthy. Pregnancy was uneventful. Birth was at term with birth weight of 3,100 g (50th centile) and length of 50 cm(50th-75th centile). Cry was high pitched. There were neonatal feeding problems. He could sit at age 2.5 years and walk at 3 years. Behavioral problems with self mutilation included trichotillomania, head banging, luxation of patellae and shoulders, and biting of other children. He developed severe scoliosis and was successfully treated by surgery.

Present examination showed a 16-year-old severely mentally retarded boy with a length of 160.5 cm (3rd centile), OFC of 50.2 cm (1 cm < 3rd centile), long, slightly asymmetric face, flat midface, epicanthal folds, synophrys, and high nose bridge. The neck was long. Bilaterally, there were simian creases and clinodactyly of the fifth fingers. There were flat feet, and walking was broad-based and clumsy. His voice was high-pitched and he could speak a few words. Cytogenetic studies of his parents were normal. Karyotype was 46,XY,del(5)(p13.3), de novo in the patient.

Patient 7

Figure 7
Patient 7: There is no microcephaly, little dysmorphism, and high pitched voice in a girl with small deletion of chromosome 5p

This 18-year-old woman (Fig. 7) is mildly mentally retarded. She was the second-born child of healthy nonconsanguineous parents. Her older brother was healthy. Pregnancy was uneventful. She was born at 38 weeks of gestation and birth weight was 2,050 g (< 3rd centile). Hypotonia was present at birth. Psychomotor development was retarded. She could walk at age 21 months. A cerebral computed tomograpy-scan was performed at age 7 years and was normal. When she was 7 years 10 months old, psychomotor examination (Termann-Merrill) showed an intelligence of 6 years 2 months. In school, there were problems with calculation skills. At age 8 years, examination showed microcephaly, small eyelashes, hypertelorism, strabismus, micrognathia, and macrostomia. Ears were large with a simple helix and everted. The metacarpals of the 4th and 5th fingers were relatively short. Speech was nasally and her voice high pitched. She had nervous behavior. Present examination showed a mildly mentally retarded female with a length of 156.3 cm (10th-25th centile), weight of 50.4 kg (1 cm > 3rd centile), OFC of 54 cm (1 cm > 3rd centile), a long face, flat midface, epicanthal folds, high palate and thin upper lip. There were bilateral simian creases and flat feet. Speech was subjectively interpreted as high-pitched, but expert logopedic examination showed a high-normal tone with hypernasality and hyperresonance. Behavior problems included nail biting, impulsivity, and disobedience. Her karyotype was 46,XX, del(5)(p15.31), de novo.

DISCUSSION

Clinical

The manifestations of the cri du chat syndrome are well known in newborn infants and include prenatal growth retardation, low birth weight, microcephaly, hypotonia, and cat-like cry. Poor suck, vomiting, failure to thrive, respiratory distress, and jaundice are present in 60 to 92% of the cases [Oosterwijk et al., 1987; Wilkins et al., 1983]. Several cardiac abnormalities are described and include atrial septal defect, ventricular septal defect, tetralogy of Fallot, and persistent ductus Botalli [Oosterwijk et al., 1987; Wilkins et al., 1983]. The phenotype in infancy and young children include psychomotor retardation, high pitched cry, microcephaly, growth retardation, poor weight gain, round face, hypertelorism, broad nasal bridge, downward slanting palpebral fissures, and micrognathia [O'Brien and Yule, 1995]. Gastrointestinal abnormalities include malrotation and Hirschprung disease [Wilkins et al., 1983]. With advancing age the phenotype becomes less striking, however, marked growth retardation continues into adulthood with resulting short stature, poor weight gain, and significant microcephaly. The face lengthens, the hypertelorism and epicanthus attenuate, and the mandibular hypoplasia becomes less evident. Teeth are decayed and abnormally erupted. The palate is high arched [Niebuhr, 1978a; Wilkins et al., 1980; Breg et al., 1970; Wilkins et al., 1983; O'Brien and Yule, 1995]. Hair is prematurely gray. There are short metacarpals and metatarsals, scoliosis, small wings of the ilia and pes planus, clubfeet, costal and vertebral anomalies [Breg et al., 1970; O'Brien and Yule, 1995]. Hypertonia of the limbs with strong reflexes and spastic broad-based gait, with bent knees, appear [Platt and Holmes, 1971]. Coordination problems are common [Colover et al., 1972]. Cerebral anomalies include atrophy of the brainstem predominating at the pontine level, small cerebellum, atrophic middle cerebellar peduncles and cerebellar white matter, and hydrocephaly [Tamraz et al., 1993]. Kjaer [1998] and Kjaer and Niebuhr [1999] reported on abnormal profile radiographs on the skull with malformed dorsum sella and cerebellar hypoplasia. Optic atrophy, cataract, and myopia were found in older patients [Breg et al., 1970].

During the first year of life there is approximately 10% mortality because of respiratory or cardiac complications [Niebuhr, 1978a; Schinzel, 1984]. Several chronic complications as upper respiratory tract infections, otitis media, and severe constipation are present [Wilkins et al., 1983].

Because of the laryngeal abnormalities, retrognathia, high palatal vault, and hypotonia, anesthetic risks are present [Yamashita et al., 1985].

Our seven patients were ranged in age from 16 to 47 years and at least three of them had a de novo deletion (Table I). Comparing their phenotype at several ages, a change of their phenotype was noted (Figs. 1-7). Birth weight was often low, and a high pitched cry was present. Almost all had feeding difficulties. At an older age these feeding difficulties were still present. All patients were severely to profoundly mentally retarded except patient 7 who was mildly mentally retarded.
Spasticity was present in two patients, however in patient 1 there was a history of birth asphyxia and in patient 5 spasticity occurred after surgery for severe scoliosis. Other patients had a clumsy, ataxia-like broad based gait. Microcephaly was present in all patients except patient 7. A cerebral computed tomograpy-scan was performed in only two patients and showed in patient 2 dilatation of the lateral ventricles and widened basal cisternae. Epileptic seizures were not present. In most patients the craniofacial traits changed with advancing age resulting in lengthening of face, large ears, macrostomia, large mandible, and prematurely gray hair. Palpebral fissures were downward slanting in children but were normal in these adults. Short metacarpals, clinodactyly of the fifth fingers, and simian creases were often present. Scoliosis was present in four patients.

There were no patients with cardiac problems, sleeping disorders, and constipation. Pubertal development was normal in our group of patients, except for patient 6 who was now starting puberty. The three female patients had normal menstruation.

The diagnosis was difficult to make in some patients who were first seen at an older age. In some of them, when clinically seen for the first time, the craniofacial appearance resembled that of Angelman syndrome.

In the present study, all except patient 1 were able to speak a few words. In the females the tone of the voice seemed high pitched, however expert logopedic studies in patient 7 demonstrated that the tone was high-normal but that hypernasality and hyperresonance were subjectively interpreted as high pitching. The voice in the adult males was normal, except in patient 6, who was now starting puberty.

In a study performed by Granoff and Preston [1971] to investigate the 'cri' by narrow-band spectrograms, they concluded that children with cytomegaly, hydrocephalus internus, or hyperbilirubinaemia do have a similarly high-pitched tone. Piérart and Remacle [1996] examined a boy of 12 ½ years with the cri du chat syndrome and found no phoniatric abnormalities. In contrast, Romano et al. [1991] described a boy and a girl whose voice was 1 and 2 octaves, respectively, above the normal age-matched values.

Development and behavior

All patients included in the present study were severely to profoundly mentally retarded, except patient 7 who was mildly mentally retarded. All except for patient 1 were able to speak a few words. Their personality was pleasant. They were interested in their environment, and they did like to have contact with others. However, there were periods of destructive behavior and aggression. Most of these periods were related to the inability of expression. In childhood the problem of self mutilation, head banging, scratching, biting, and cruelty to others was often severe. With advancing age these problems decreased, they did like teasing and were often hyperactive. In two patients hypersensitivity to sound was present.

Behavior problems are reported in about 30% of the patients with hyperactivity, irritability, and self-stimulation [Oosterwijk et al., 1987; Wilkins et al., 1980]. Cornish and Pigram [1996] reported a first optimistic study on the behavior phenotype in the cri du chat patient and described the most striking characteristics including self injury, repetitive movements, obsessive attachment to objects, hypersensitivity to sensory stimuli, stubbornness, clumsiness, autistic disturbances, feeding- and sleeping problems, and mood disorders. They reported a low incidence of hyperactivity. Gross hand movements were better developed than fine hand movements, and speech was deficient although over 50% of the patients were able to use sign language. The cri du chat children who received early introduction to special programs were ambulatory, developed many self-care skills, and could communicate either verbally or through gestural language. Although these children did have severely compromised mental capacities, they did benefit from early, intensive programs of special education [Wilkins et al., 1980]. Clarke and Boer [1998] reported greater problems with overactivity and restlessness in patients with cri du chat syndrome than found by Cornish and Pigram [1996].

We conclude that stimulation programs should include forms of communication training to prevent self mutilation and behavior problems.

Genotype-phenotype correlation

The critical region of typical cri du chat phenotype is caused by a deletion of the band 5p15.2 [Simmons et al., 1995]. Previous reports indicated that about 80% of the de novo deletions are of paternal origin [Overhauser et al., 1990]. In most of the patients in the present study, except patient 7, large 5p deletions were found and all patients, except patient 7, were severely to profoundly mentally retarded (Fig. 8). In patients 2, 3, 5 and 7 further chromosome microdissection investigations were performed to rule out interstitial deletions and to study de novo telomere synthesis [Vermeesch et al., 1998]. Patients with more distal 5p(15.3) deletion are minimally

Figure 8
Chromosomal result of each patient, except for patient 1, is compared with the idiogram of chromosome 5. A: Note the rather large deletions in all but patient 7. B: The black bar represents the location of absence of chromosomal material

delayed and have a much better prognosis. The proximal part of the 5p15.3 region seems to be associated with the cat-like cry [Overhauser et al., 1994; Gersh et al., 1994; Gersh et al., 1995]. However, Church et al. [1995] concluded that there was no correlation between the size of the deletion and the severity of mental retardation. Patient 7 has a small deletion del(5)(p15.31) and has a milder phenotype with normal head circumference. This may indicate that the critical region for microcephaly, one of the major characteristics of the cri du chat syndrome, is located more proximal than 5p15.31.

Recently several genes were mapped at the cri du chat candidate interval [Simmons et al., 1997; Simmons et al., 1998]. The human Semaphorin F (*SEMAF*) gene is a member of a family of proteins that possibly play a role in axonal pathfinding during embryonic development and is expressed in mice on the ventricular zone of the cortex and the basal ganglia. Soon after leaving the ventricular zone, postmitotic neurons stop expressing *SEMAF*. Altered neuronal migration could lead to severe mental retardation and microcephaly [Simmons et al., 1998]. Recently, Kjaer and Niebuhr [1999] studied malformations of the cranial base in cri du chat patients, and indicated the existence of a developmental field between the rhombencephalic cranial brainstem and the laryngeal region from which the characteristic cry may derive. Further analysis of the function of *SEMAF* and further molecular studies of the 5p15 region are necessary in order to obtain a better delineation of the extent of the deletion and its phenotypic correlation.

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1.2.2 13q Deletion syndrome in an adult mentally retarded patient

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Abstract

Clinical features of the 13q deletion syndrome are difficult to define and include retinoblastoma, mental and growth retardation, craniofacial abnormalities, brain, gastrointestinal, renal and heart malformations, anal atresia, and limb and digit malformations. The critical region for development of major organ systems has been defined in 13q32 between the proximal marker D13S132 and distal marker D13S147. We report a severely mentally retarded male patient with a deletion of the distal part of chromosome 13 (13q32.3→qter) without major organ malformations.

Introduction

Several patients with different types of a terminal deletion of chromosome 13 i.e. ring chromosomes, terminal and interstitial deletions have been reported (1-3, 5-7, 9, 11, 12). Typical findings include mental and growth retardation, craniofacial dysmorphism including eye abnormalities such as microphthalmia and coloboma, retinoblastoma, ear abnormalities, hypoplasia or aplasia of the thumbs, heart defects, genital abnormalities and imperforate anus (6). Niebuhr and Ottosen (7) first proposed a classification in 3 groups which was later modified by Niebuhr (8) and Brown et al. (2). We describe an adult mentally retarded male and compare his findings with the published data.

Case Report

The patient is a 49 years-old severely mentally retarded male. He was the third child of healthy non-consanguineous parents. His 6 siblings were healthy.

Pregnancy was uneventful. He was born at term with a birth weight of 2,000 g. There was asphyxia. Postpartal there were feeding problems. At the age of 6 months psychomotor retardation was noticed. He could sit at the age of 2 years, walk at 4 years, and at the age of 9 years he could speak only a few words. Anisocoria was present from the beginning. At the age of 27 years he was surgically treated because of severe equinovarus of the left foot. Mental retardation was not progressive.

Present examination showed a severely mentally retarded non-ambulant male with microcephaly (50.3 cm (< 3rd centile) and short stature of 150 cm (< 3rd centile). Craniofacial features were distinct and included sloping forehead, cutis verticis gyrata, absence of the lateral eyebrows, strabismus convergens, eccentric pupils with medial deviation bilaterally, large nose, small nasal bridge, flat midface, small mouth, small mandible, large ears (Fig. 1). The neck was short and there was a low posterior hairline. A mild cutaneous syndactyly of the second and third toes was present. Neurological examination showed hypertonia of the extremities and thoracic scoliosis. There was no speech. A CT-scan of the brain showed mild asymmetry of the ventricles. Cervical radiographs and myelography showed congenital fused vertebrae C3-C4 and C4-C5 and stenosis of the cervical canal C4-C5-C6-C7 with bilateral radix compression C5-C7.

Figure 1
The distinct craniofacial appearance with long face, sloping forehead, absent lateral eyebrows, strabismus convergens, eccentric pupils, large nose, flat midface, small mouth, small mandible, and large ears

Cytogenetic Studies

Chromosomal studies on peripheral blood lymphocytes were performed according to standard cytogenetic techniques, and included G-banding. Cytogenetic analysis in all investigated metaphases revealed a deletion of the long arm of chromosome 13. The proband's karyotype was 46,XY,del(13)(q32.3→qter) (Fig. 2). Chromosomal studies of both parents were normal.

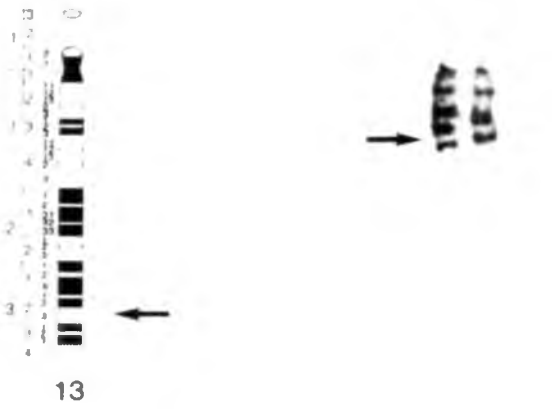

Figure 2
Chromosome 13 (one cell; G-banding). The arrows indicate the deletion at band 13q32.3, on the normal chromosome 13, and on the schematic representation of chromosome 13

Discussion

Several phenotypes have been associated with 13q- monosomy as a result of different chromosomal abnormalities varying from ring chromosomes, interstitial deletions and terminal deletions, often complicated by mosaicism or partial trisomy (8, 10). Therefore, diagnostic findings were difficult to define and include retinoblastoma, mental and growth retardation, craniofacial abnormalities, brain, gastrointestinal, renal and heart malformations, anal atresia, and limb and digit malformations (2). Niebuhr and Ottosen (7) were the first to propose a classification for patients with a 13q deletion in 3 groups, which was later revised by Niebuhr (8) in 4 categories on the basis of physical and cytogenetic findings with the observation that those patients with distal deletions were the most severely affected and those with more proximal deletions tended to have fewer major anomalies,

except for retinoblastoma. Brown et al. (2) noted that among his own patients as well as those in the literature, only those with deletions of band 13q32 had severe malformations and proposed the following classification: group 1 comprises patients with a proximal deletion, usually not extending into 13q32. In this group, patients have mild to moderate mental retardation, variable dysmorphic features, and growth retardation. Retinoblastoma can be present, depending on the deleted segment. Group 2 include patients with a more distal deletion including at least a part of 13q32, and they present major malformations including severe mental and growth retardation, severe microcephaly, brain malformations (posterior encephalocoele and holoprosencephaly), absent thumbs or other distal limb abnormalities, eye malformations (severe microphthalmia, retina colobomata), genitourinary and gastrointestinal tract malformations. Group 3 patients have distal deletions (13q33 or 13q34) and are severely mentally retarded, but without other major malformations or growth retardation.

The present patient shows a deletion of the distal part of chromosome 13q32.3→qter. Therefore he fits in the second group of the proposed classification. He has normal limb development with no absent thumbs. Turleau et al. (12) reported a 14 month-old boy with mild dysmorphic features, including growth retardation, microcephaly, brachycephaly, round and flat face, slight upward slanting palpebral fissures, small mouth, large ears, small penis and hypospadias and moderate mental retardation (IQ= 64), who has a de novo deletion of 13q33→qter. Telfer et al. (11) reported mild dysmorphic craniofacial features including facial asymmetry, hypertelorism, ptosis, wide nasal bridge, protruding upper incisors, large ears, bilateral hearing loss, microcephaly, delayed psychomotor development, severe mental retardation, hypoplastic thumbs, talipes equinovarus, hemivertebrae at L3 and L4 and partial absence of the corpus callosum in an 8 years-old female with a deletion of 13q32→qter. Rivera et al. (9) reported 2 patients with a 13q32.3→qter deletion. The first patient was a 5 months-old female baby with delayed development, low posterior hairline, large ears with overdevelopped lobules, weak cry, slender fingers, sacral dimple, muscular hypotonia, abnormalities of the D3 vertebral body, and a 13q deletion as the unbalanced product of a maternal translocation (8;13)(q24.3;q32.3). The second patient was a 2 years 7 months-old female with retarded development, hypertrichosis, muscular hypotonia, narrow forehead, prominent metopic suture, synophrys, epicanthal folds, slender fingers and broad first toes.

A critical deletion region in band 13q32 which contains one or more genes crucial for brain, digit and other organ development was hypothesized by Brown et al. (2). Brown et al. (3) proposed that the region in 13q32 in all of the severely

affected patients can be defined as bounded proximally by marker D13S132 and distally by marker D13S147, critical for development of major organ systems. Recently, Guala et al. (4), described a patient with a ring chromosome 13 with loss of the region D13S317-D13S285 with mental retardation and multiple congenital anomalies including facial abnormalities, agenesis of the corpus callosum, heart defect, ambiguous genitalia and abnormalities of the first ray of the upper limb; his phenotype overlaps a previous description of the XK aprosencephaly syndrome suggesting that patients with this syndrome and apparently normal cytogenetic findings, should be further studied at the molecular level of the critical region identified by Brown et al. (3). Veugelers et al. (13) characterised the gene for a novel proteo-glypican (GPC5) mapping to 13q32 which is expressed in brain tissue of the adult, suggesting a potential role in the control of neurotrophic factors and the maintenance of neural function. Expression of the gene in embryonic tissue suggests that the expression of glypican-5 may be developmentally regulated, with a potentially more general role in the control of growth and differentiation during mammalian development. An interesting finding is that postaxial polydactyly occurs almost exclusively with trisomy 13 whereas deletion 13q, with the critical segment in 13q31-q34, where GPC5 appears to be localised, is associated with oligodactyly and bony syndactyly of thumbs and first metacarpals.

The phenomenon of imprinting can complicate the analysis of deletions, since the parental origin of the deletion could affect the observed phenotype, if the deleted region is imprinted. There are several reasons for believing that chromosome 13 is not imprinted and that imprinting does not play a role in the observations made by Brown et al. (3) since patients with maternal uniparental disomy, and normal phenotype were reported. Furthermore, 13q deletions both of maternal and paternal origin have been reported in patients with absent thumbs and brain malformations.

In conclusion, further molecular studies to narrow the critical region within 13q32 are needed, in order to obtain more precise data in the study of the genotype/phenotype correlation of this chromosomal region.

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1.2.3 ANGELMAN SYNDROME IN THREE ADULT PATIENTS WITH ATYPICAL PRESENTATION AND SEVERE NEUROLOGICAL COMPLICATIONS

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ABSTRACT

Angelman syndrome (AS) is a distinct neurogenetic disorder and the phenotype is well known in childhood and adolescence. However, with advancing age the clinical and behavioral phenotype changes. In adulthood, the phenotype can be rather aspecific. We report on AS in 3 severely to profoundly mentally retarded patients, who developed severe neurologic complications of severe tremor, spasticity and coordination problems, resulting into severe loss of function. They presented atypical craniofacial features, short stature, epileptic seizures, microcephaly, brachytelephalangy and absent speech. Two patients presented at an older age a change in day-night rhythm. Based on this experience, we conclude that all severely to profoundly mentally retarded patients with atypical phenotype, spasticity, absent speech, epileptic seizures and changed day-night rhythm are candidates for further cytogenetic and molecular investigation for AS. Clinical photographs of the patient at a younger age can be helpful. The presence of the typical EEG pattern with frontal triphasic delta waves may direct to the diagnosis of AS.

INTRODUCTION

Angelman syndrome (AS) (MIM 105830) is a distinct neurological disorder, for the first time described in 1965 (1) in 3 non-related mentally retarded children, and is caused by the loss of function of imprinted genes in 15q11-q13 (4, 22). The *UBE3A* gene has been found to be mutated in several AS patients (16, 21, 22). AS

presents with severe mental retardation, short stature, absent speech, inappropriate periods of laughter, microcephaly, macrostomia, maxillary hypoplasia, prognathia, ataxia, and epileptic seizures, with specific EEG pattern (26). With advancing age, the typical phenotype becomes less striking due to coarsening of the face, thoracic scoliosis and decrease of mobility (5, 18). The bursts of laughter are less frequently than in childhood (18). Epileptic seizures are still present in adult AS patients (18). Children and adults have a happy and excitable personality often with hand flapping movements and are attracted to and fascinated with water. With advancing age the hyperactivity, short attention span, and sleeping problems improve (7, 26, 28).

We report on three severely to profoundly mentally retarded patients with AS, confirmed by molecular studies, who presented severe neurological complications of spasticity, atypical craniofacial features, changed day-night rhythm and brachytelephalangy.

CASE REPORTS

Patient 1 (P.H.)

The patient is a 52-year-old severely mentally retarded male. Family history revealed two maternal aunts with mild mental retardation and one other maternal aunt with epileptic seizures. His parents and brother were healthy. During pregnancy maternal hypertension was present. Birth was uncomplicated and birthweight was 3,500g. Retardation was first noticed at the age of 1 year. He developed no speech. At the age of 2 years microcephaly was noticed. He was institutionalized at the age of 7 years and neurological examination revealed a slow and rigid boy with obsessive mimicking and poor motor development. He had no speech and produced only noises. Clinical examination at the age of 15 years revealed slow tremor in the upper extremities, hyperreflexia in the upper and lower extremities and rigidity. At the age of 27 years walking was clumsy, and tremor of the upper extremities and frequent bursts of laughter were present. Epileptic seizures of the grand mal type were present at the age of 39 years. He received anti-epileptic drugs (carbamazepin and sodium valproate). Baclofen was given because of a slow tremor of both hands. Spasticity of the lower extremities was present and clonus of the achilles tendon. Mouth was large and palate asymmetric. At the age of 51 years progressive loss of function was noticed. Slow tremor of hands and arms were still present and also constant movements of the tongue. Walking was slow and atactic. An EEG showed frequent paroxysms typical for epileptic activity. MRI of the cerebrum showed discrete cerebellar atrophia. On the

right occipital region an old small infarct zone was present and a gliotic zone on the left frontal region. Cervical spine MRI showed bulging discs on levels C3-C4, C4-C5 and C5-C6.

Examination at the age of 52 years showed a severely mentally retarded male with a height of 161 cm (1cm < 3rd centile), weight of 67.5 kg (75th centile), and head circumference of 51.4 cm (1.5 cm < 3rd centile). Craniofacial features included brachycephaly, large ears, macrostomia, narrow palate, normal teeth, and large mandible (Fig. 1 and 2). Scoliosis was present. He had relatively short fingers with flat, broad, and short distal phalanges (Fig. 3). Neurological examination revealed tremor of the upper extremities. He was wheel chair bound because of very severe clumsy walking and spasticity of the lower extremities. Speech was absent. At the age of 52 years, the diagnosis of AS was confirmed by DNA studies (probe PW7.1B). Distinction between maternal deletion and paternal uniparental disomy was not made. Cytogenetic studies on peripheral lymphocytes, according to standard procedures, revealed a normal male karyotype 46,XY. Screening for inborn errors of metabolism, included amino acids, organic acids, purine and pyrimidine metabolism and lysosomial disorders and revealed uraciluria, hypoxanthinuria and xanthinuria.

Figure 1
Microcephaly, maxilla hypoplasia, large mouth, prognathia and large ears in patient 1

Figure 2
Brachycephalic skull in patient 1

Figure 3
Spatula-like distal phalanges of patient 1

Patient 2 (K.S.)

This patient is a 32-years-old profoundly mentally retarded female. Family history was negative for mental retardation. Her parents were unrelated. During pregnancy there was threatened abortion. She was born at 39 weeks. Birth weight was 3,200 g and length 53 cm. Three weeks postpartal, she was hospitalized because of severe vomiting. She suffered from frequent upper respiratory tract infections and from otitis media. At the age of 2 years she developed epileptic seizures, with grand mal and petit mal. There was psychomotor retardation: she could sit at the age of 1 year, and at the age of 2.5 years she could speak only 2 words. She was never ambulant. At 6 years height was 106 cm (< 3rd centile), weight 18 kg (10th centile) and head circumference 48 cm (< 3rd centile). Craniofacial features included brachycephaly, asymmetric face, large mouth, high palate, gingival hyperplasia. Neurological examination revealed left-sided hemispasticity. At the age of 13 years, length was 150 cm (10th to 25th centile), weigth 42.6 kg (25th to 50th centile) and head circumference 50 cm (< 3rd centile). There was spastic quadriplegia with contractures more severe on the left side. She developed dextroconvex scoliosis. Distal dystrophia and hypotrophia was present at the age of 17 years 7 months. At the age of 29 years a change of the sleep pattern was present: during the day she fell asleep, in the evening she wanted to go sleep early, and during the night she awakened early. An EEG, performed during a period of sleep, showed no specific abnormalities. Perinatal complications resulting in

cerebral palsy were thought to be the cause of the mental retardation and neurological problems in this patient.

Present examination showed a profoundly mentally retarded female with a height of 150 cm (< 3rd centile), weight 51 kg (25th centile), head circumference 50.5 cm (< 3rd centile). Craniofacial features included brachycephaly, nuchal webbing, midfacial hypoplasia, large mouth, blond hairs, and blue eyes (Fig. 4 and 5). Thorax was asymmetric and scoliosis was present. Neurological examination revealed a non-ambulant female with generalized tremor, axial hypotonia, hyperreflexia of the lower limbs (L>R), hypertonia (L>R) and distal hypotrophia of the hands and feet. The distal phalanges of both hands were short and broad (Fig. 6). Contractures of elbows, fingers, knees and feet were present. Periods of frequent

Figure 4
Maxillary hypoplasia, thin upper lip and poor facial expression in patient 2

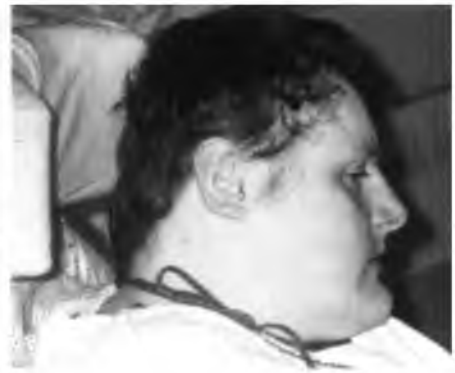

Figure 5
Brachycephaly and prognathism in patient 2

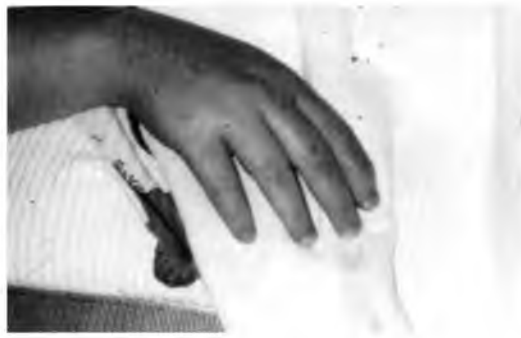

Figure 6
Note the short distal phalanges in patient 2

laughter were present. Epileptic attacks were treated by sodium valproate. Because of the change of day-night rhythm the diagnosis of AS was considered at the age of 29 years, and was confirmed by DNA analysis (probe PW7.1B), without distinction between maternal deletion and paternal uniparental disomy. Routine cytogenetic studies on peripheral lymphocytes showed a normal female karyotype, 46,XX.

Patient 3 (D.V.O.)

This patient is a 49-year-old severely mentally retarded female. Family history revealed no mental retardation, but 4 of her sibs died soon after birth and there were 4 miscarriages. At 28 months, epileptic seizures were present. Speech was absent. At the age of 28 years, she was institutionalized. Clinical examination showed height 153 cm (3rd centile), weight 48 kg (3rd to 10th centile) and head circumference 52 cm (3rd to 10th centile). Craniofacial features included low anterior hairline, macrostomia with full lower lip, small teeth and caries, and prognathia. Neurological examination revealed spastic paraplegia with hypotrophia and hyperreflexia of the lower limbs. Coordination and vestibular function were poorly developed. At the age of 33 years she developed epileptic seizures and treatment with sodium valproate was started. An EEG showed frequent paroxysms of epileptic activity.

Present examination showed a severely mentally retarded female with head circumference of 52.3 cm (3rd to 10th centile). Craniofacial features included a flat occiput, light colored hairs, and macrostomia (Fig. 7 and 8). She had severe myopia.

Figure 7
Macrostomia and midfacial hypoplasia in patient 3

Figure 8
Prognathism and brachycephaly in patient 3

Neurological examination showed a semi-ambulant female with rigidity of the lower limbs and spastic walking. Mild scoliosis was present. The 5th rays of the hands were bilaterally short. The distal phalanges of the fingers were short and broad (Fig. 9). Day-night rhythm was disturbed: during the day she constantly fells asleep and is awakened early in the morning. She had frequent periods of inappropriate laughter. The diagnosis of AS was made at the age of 49 years, because of the disturbed day-night rhythm and was confirmed by molecular studies (probe PW7.1B), without distinction between maternal deletion and paternal uniparental disomy.

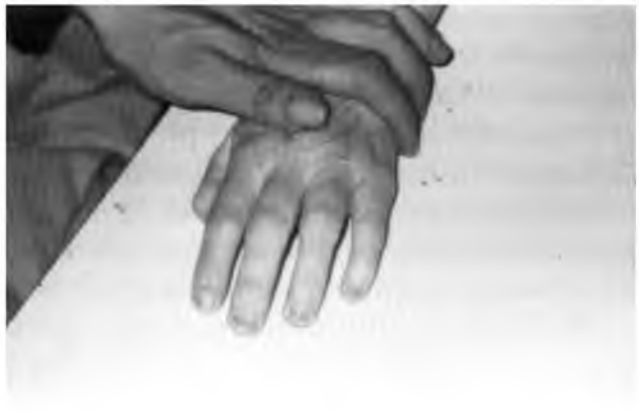

Figure 9
Short and broad distal phalanges in patient 3

Discussion

AS is a distinct neurogenetic disorder caused by the loss of function of imprinted genes in proximal 15q11-q13 (4) and the prevalence is estimated as 1 in 12,000 to 1 in 20,000 (8, 23).

The clinical features are well known in children and adolescents with severe mental retardation, severe postnatal growth deficiency, absent speech, maxillary hypoplasia, macrostomia, protruding tongue and widely spaced teeth, thin upper lip and prognathia. Ears are low-set. Strabismus, myopia and hypopigmentation of the fundus are frequent eye abnormalities. At birth, the head circumference is often within the normal range, but growth flattens and microcephaly is present in the postpartal period (5, 6). Neurological abnormalities include ataxia, truncal hypotonia with hypertonia of the limbs, laughter paroxysms and epileptic seizures

in 80 to 90%, and 10% of the patients are never able to walk independently (7, 15, 19, 24-28). In childhood, a diversity of seizures was observed: tonic-clonic seizures, atypical absence seizures, myoclonic seizures, status epilepticus and absence status, and myoclonic status (12, 19). CT-scan of the brain showed diffuse brain atrophy and MRI indicated in 50% of cases a disturbance in the developmental process early in embryogenesis (2, 11, 14). The behavioral phenotype in children is a happy and excitable personality often with hand flapping movements, hyperactivity, without aggression, short attention span, sleeping problems with decreased need to sleep, increased sensitivity to heat, attraction to and fascination with water (7, 9, 13, 14, 26, 28).

With advancing age the clinical picture changes: in adults marked prognathism, macrostomia and a prominent lower lip is present. The cause of coarsening of the face is not known and is found both in patients with and without anti-epileptic drug therapy. Thoracic scoliosis is frequently present and mostly in females. Mobility decreases with advancing age, with difficulties of walking and some patients become wheel chair bound. Matsumoto et al. (20), Viani et al. (25) and Clayton-Smith (7) report on decrease of the epileptic seizures with advancing age and Clayton-Smith (7) and Boyd et al. (3) reported that the typical EEG findings in AS patients in childhood do not occur in adult patients. However, Laan et al. (19) observed that 92% of the adult patients still experienced epileptic seizures, with atypical absence seizures and myoclonic seizures being the most prominent. The most typical EEG finding in AS, both in children and adults, was the presence of triphasic delta activity with a maximum over the frontal regions. The probability of having triphasic waves increased with age. In mentally retarded patients this EEG pattern can be helpful for the diagnosis of AS and differential diagnosis includes hypsarrhythmia in the West syndrome or the petit mal variant pattern in Lennox-Gastaut. Paroxysms of laughter are present but less frequent than in childhood (5, 18). The behavioral phenotype in adults includes happy disposition, curiosity and stubbornness, but less frequent hyperactivity, and attention span is longer than in childhood. Zori et al. (28) reported improvement of sleeping problems with age. There is attraction to water and they like watching television and looking at magazines. Adults do not speak more than 6 words, and expression is nonverbally by using gestures (5, 18).

Neurological complications of spasticity and tremor in patient 1 were severe and a progressive loss of function was present until he became wheel chair bound. The cause of his mental and neurological problems was thought in the past due to a birth complication. The diagnosis of AS was made after an extensive clinical examination at an older age of the patient. Uraciluria, hypoxanthinuria and xanthinuria was

explained by anti-epileptic drug therapy.

In patient 2, the clinical diagnosis of AS was confirmed by molecular studies at the age of 29 years. In this patient perinatal complications resulting in cerebral palsy were considered as the cause of the mental retardation and the severe neurological status of the patient. At the age of 29 years, a change in day-night rhythm was observed and this was an indication for further investigations.

Spastic paraplegia and poorly developed coordination and vestibular functions were present in patient 3. The etiology of the mental retardation was unknown for a long time. At the age of 49 years a disturbed day-night rhythm was present, and, at that time, further investigation of the patient was started. Clinical photographs of the patient at a younger age were helpful in making the diagnosis.

All 3 patients had rather typical short and broad distal phalanges of both hands. We may conclude that the phenotype of AS can be very difficult to diagnose in older patients, certainly when severe neurological complications are present and have affected the phenotype. Patients with severe spasticity, without speech and with epileptic seizures, with the diagnosis of "birth complication" or "perinatal complication" need certainly cytogenetic studies completed by molecular studies for AS. Clinical photographs of the patient at a younger age and the typical EEG pattern can be helpful in making the diagnosis (10, 13, 17, 19).

The presence of the atypical craniofacial features, severe neurologic complications, change in day-night rhythm, and brachytelephalangy was striking in our patients and further observations are needed to confirm these features in AS adults.

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CHAPTER 2
X-LINKED MENTAL RETARDATION

Content Chapter 2

2.1 THE CLINICAL PHENOTYPE IN INSTITUTIONALISED ADULT MALES WITH X-LINKED MENTAL RETARDATION (XLMR)

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ABSTRACT

In an institutionalised population of 471 mentally retarded adult residents (436 males and 35 females), 22 males (i.e. 5% of the male population) had XLMR, accounting for 36.1% of the residents diagnosed with a monogenic disorder (n=61). Fragile X syndrome (FRAXA) was diagnosed in 16 residents, X-linked mental retardation with marfanoid habitus (Lujan-Fryns syndrome) in 2, and non-specific X-linked mental retardation (MRX) in 4 males. The 4 MRX-patients included 3 male sibs of a family, carrying a mutation in the IL-1 receptor accessory protein-like gene, and one male patient member of the MRX-44 family (linkage with LOD-score of 2.90). In the group of 215 males with idiopathic mental retardation (MR), family histories and pedigree data were compatible with XLMR in 35 males (35/215= 16.3%) from 32 families. Of these 35 males, 5.7% were microcephalic with dysmorphic features and 5.7% macrocephalic; micro-orchidism and macro-orchidism were each found in 11.4%. One macrocephalic male had also macro-orchidism and dysmorphic features. In this study, the diagnosis of XLMR could thus be proposed in 57 males i.e. 13.1% of the total male population. The clinical phenotype, behavioural problems, and follow-up data in these different subgroups of XLMR are presented.

INTRODUCTION

X-linked mental retardation (XLMR) is estimated to account for 20 to 25% of all mentally retarded males and for 10% of mildly mentally retarded females (20, 30, 32). XLMR conditions are categorised as syndromic (MRXS) if associated with characteristic clinical features, or non-specific (MRX) if MR is the only symptom

in affected individuals. The most frequent entity in the group of syndromal XLMR (MRXS) is the fragile X syndrome, occurring in approximately 1/4,000 to 1/6,000 in males, and accounting for 15 to 20% of XLMR in males (6, 27). The nosology of non-specific X-linked mental retardation (MRX), that constitutes two thirds of all XLMR, is much less well defined. Recently, 8 genes involved in MRX have been identified, but these account each for only 0.5% to 1% of all MRX patients (1, 2, 4, 5, 7, 14, 15, 18, 23, 34).

An overview of all patients with syndromal and non-specific XLMR diagnosed in an adult male population of 471 institutionalised mentally retarded residents is presented.

Materials and Methods

During the systematic etiological survey in the institution for the mentally retarded "Huize Assisië", Udenhout, The Netherlands, the group of patients with XLMR, with either, MRXS or MRX, was further evaluated. Patient records were studied and a written permission to perform a physical examination, cytogenetic and molecular studies, and screening for inborn errors of metabolism was obtained from the legal representative of patients who were never examined before. Family data and medical data were collected by a questionnaire. Mental retardation (MR) in one or both parents, one or more sibs, or own children was considered as first degree familial MR. In second degree familial MR one or more uncles or aunts, nieces or nephews were mentally retarded. All patients were psychologically tested by standard methods to estimate the mental level. The occipital-frontal circumference (OFC) was defined in males with 3rd centile = 53 cm and 97th centile = 58 cm and in females 3rd centile = 52 cm and 97th centile = 56.5 cm (24, 28). These figures were corrected for height according to Bushby et al. (3). The OFC was compared with the testicular volume. Macro-orchidism was defined as a testicular volume $\geq$ 25 ml and micro-orchidism as a testicular volume $\leq$ 10 ml (16).

Cytogenetic studies were performed on cultured peripheral lymphocytes, according to standard procedures. In all clinically suspected fragile X patients, GTG-banding after culturing in folic acid poor medium (22) was performed in the past and assessment of the CGG expansion mutation in the FMR-1 gene was done. Genetic linkage studies were performed in these families with pedigree data suggesting X-linked mental retardation.

RESULTS

Twenty-two males (5% of the male population) were found to have XLMR, accounting for 36.1% of the monogenic disorders (n=61) diagnosed in this institution (33). In 35 other residents with non-specific phenotype, pedigree data were suggestive for XLMR. Table I presents the classification of these 57 male residents according to MRXS, MRX and male patients with idiopathic MR and pedigree data compatible with the diagnosis of XLMR.

Table I: Classification of all males with XLMR, and males with idiopathic MR and familial MR

XLMR	MIM number	Diagnosis	Number of patients (n)	Comment
MRXS				
	*309550	Fragile X syndrome	16	1 with Prader-Willi syndrome-like phenotype
	*309520	Lujan-Fryns syndrome	2	
MRX				
		Family with IL1RAPL gene mutation (locus Xp22.1-21.3)	3	3 sibs from 1 family
		MRX44 family (Xp11.3-p11.21)	1	
Idiopathic MR and familial MR				
		First degree relatives	63	Maternal MR: 32 (XLMR) Paternal MR: 6 Not conclusive: 25
		Second degree relatives	6	Maternal MR: 3 (XLMR) Paternal MR: 1 Not conclusive: 2

1. Syndromic XLMR (n=18)

1. Fragile X syndrome (n=16) (Tables I and II)

Fragile X syndrome (MIM *309550) was diagnosed in 16 males, including 2 brothers (Table II). Eleven residents (68.8%) were older than 40 years of age. Ten (62.5%) were moderately and 6 (37.5%) severely mentally retarded. Epileptic seizures were present in 5 (31%). Three patients suffered from very severe vision

Table II: Clinical features in the patients with fragile X syndrome

Case (yrs)	Age at diagnosis (yrs)	MR	Epilepsy	Clinical features	Behavioural phenotype	Vision	Hearing
1 (14)	3	Moderate	+	SS, obesity, short broad hands and feet, hypogenitalism	Shy Aggression Difficult	N	N
2 (45)	?	Moderate	+	Long face	Avoids contact	Severe loss	N
3 (53)	?	Severe	+	Long face	Avoids contact	N	Moderate loss
4 (55)	47	Moderate	-	Long face	Avoids eye contact Aggression Destruction	N	N
5 (62)	62	Severe	-	SS Long face	Coarse movements Hyperactive Difficult	Severe loss	Moderate loss
6 (58)	50	Severe	-	Long face Large mandible	Avoids eye contact	N	N
7 (31)	19	Severe	+	Long face Macrocephaly Flat feet	Hyperactive Speech delay Hyperactive Difficult Handbiting	N	N
8 (47)	47	Moderate	-	Macrocephaly Macrotestes Long face Large mandible Inguinal hernia	Avoids eye contact Hyperactive	N	N
9 (48)	?	Severe	-			N	Moderate loss
10 (39)	26	Moderate	-	Long face Large mandible	Avoids eye contact	N	N
11 (48)	35	Moderate	-	Large mandible	Hyperactive	N	N
12 (46)	33	Moderate	-	Long face Large mandible	Shy	N	N
13 (35)	24	Moderate	-	Large mandible	Difficult	N	N
14 (61)	51	Severe	-	Large mandible		N	N
15 (69)	59	Moderate	+	Long face Large mandible		Severe loss	Mild loss
16 (31)	18	Moderate	-	Long face Inguinal hernia Neonatal vomiting	Hyperactive	N	N

N: normal; +: Present; MR: mental retardation; SS: short stature

loss, and 3 patients had moderate hearing loss. A 45-year-old male had divergent strabismus and myopia with onset at the age of 20 years. A 62-years-old male had divergent strabismus, papillary atrophy and moderate hearing loss. A 69-year-old male suffered from bilateral cataract and presbyacusis. Typical clinical features i.e. long face, large mandible, and macro-orchidism, were present in all patients. They were shy and avoided eye contact, and behavioural problems included hyperactivity, self mutilation with hand biting and aggression. One patient showed Prader-Willi syndrome-like phenotypic features (Table II).

2. X-linked mental retardation with marfanoid habitus (Lujan-Fryns syndrome) (MIM*309520) (n=2)

Two moderately mentally retarded males presented the association of moderate mental retardation, ectomorphic habitus and shy behaviour (Table I). Chromosomal studies were normal 46,XY, and a FMR-1 expansion mutation was not found. Screening for inborn errors of metabolism showed no abnormalities and homocystinuria was excluded in both patients. Also Marfan syndrome was excluded since ophthalmologic and cardiac examination revealed no abnormalities.

Patient 1 (Figs. 1A and 1B)

The first patient was 43 years old. Psychomotor development was retarded and he could walk age 2 years. From age 12 years, walking became progressively difficult. Head circumference was 52.8 cm (3rd centile), height 191.5 cm (>97th centile) and span 189 cm. His face was long and his voice was hypernasal. There

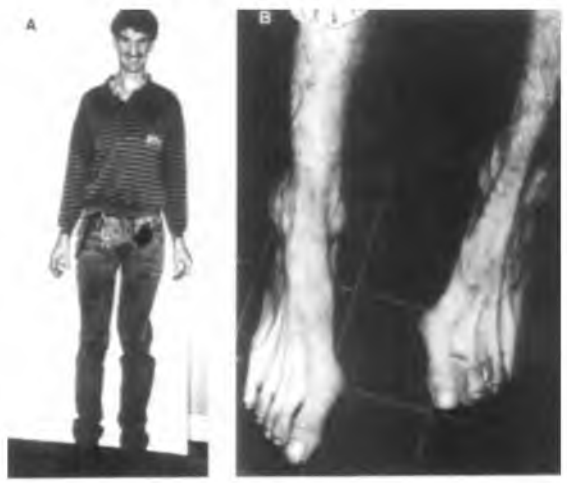

Figure 1A and B
Note the ectomorphic habitus, long face and small feet in the moderately mentally retarded patient with X-linked MR and marfanoid habitus

was pectus carinatum and spasticity of the lower limbs. He was very shy and had autistic-like behaviour. There was no history of psychosis.

Patient 2

The second patient was a 41-year-old male. There was no family history of mental handicap. Birth was uneventful and psychomotor development was delayed. During childhood he was clumsy and had co-ordination problems. Examination revealed head circumference of 59.2 cm (>97th centile), height 190 cm (>97 centile) and span of 184 cm. Craniofacial features included downward slanting palpebral fissures, large mandible, high palate, and myopathic face. Walking was ataxic and broad-based. Finger joints were hyperextensible. He was very shy. MRI of the brain showed minimal cerebellar atrophy.

2. Non-specific X-linked mental retardation (Table I) (n=4)

1. Clinical description of the family with IL1RAPL gene mutation (IL-1 receptor accessory protein like)(Xp22.1-21.3)

Three mentally retarded brothers (Fig. 2) of one family were residents in this institution. The 3 index-patients (II-4, II-6 and II-7) are indicated on the family pedigree (Fig. 3). Chromosomal studies were normal 46,XY and screening for FMR-1 triplet expansion was normal in all 3 patients. Parents were

Figure 2A, B & C
The non-specific phenotypic presentation of the 3 affected brothers, from the small MRX family with a non-sense mutation in the IL1RAPL gene

nonconsanguineous and there was no family history of MR. The oldest girl (II-1) had a history of depression. A second female (II-2) was moderately mentally retarded but no further information was available. A male child (II-3) died at the age of 9 months after complications of encephalitis. II-5 is mentally normal and has one healthy daughter (III-1). There were 3 miscarriages (II-8; II-9; II-10). In the 3 affected brothers, from this small MRX family, a non-sense mutation in the IL1RAPL gene resulting in a premature stop codon, was found (4).

Patient 1 (II-4) (Fig. 2A)

This male was 62 years old and moderately mentally retarded. Pregnancy was uneventful. He was born at term. There was periodic difficult and hot-tempered behaviour. Present examination showed length 173.5 cm (25-50th centile), weight 68 kg (50-75th centile) and head circumference 55 cm (50th centile). The skin was soft. Craniofacial features included flat occiput, narrow eyelashes, nystagmus, and grooved tongue. His voice was specific with high pitch and hypernasality. The thorax was small and testes were normal. Neurological examination revealed clumsy walking and hypotrophy of the lower legs.

Patient 2 (II-6) (Fig. 2B)

This severely mentally retarded male was 59 years old. Pregnancy was uneventful. He was born at term and birth weight was 4,000g. There were feeding difficulties with frequent vomiting in the neonatal period. At the age of 1 year, he was hospitalised because of meningitis. Behavioural problems included self mutilation, screaming and destroying objects. At age 55 years there was bilateral moderate hearing loss. Present examination showed height 162.5 cm (<3rd centile), weight 70.2 kg (50-75th centile) and head circumference 55.8 cm (50-75th centile). Span was 173 cm. The skin was soft, with striae on the upper limbs. He could speak some words with a hoarse and hypernasal voice. Craniofacial features included flat occiput, mild facial asymmetry and grooved tongue. Testes were small. Neurological examination showed clumsy walking and the toes were upright. He was friendly and social. Language comprehension was better developed than active speech.

Patient 3 (II-7) (Fig. 2C)

This patient is 54 years old and moderately mentally retarded. Pregnancy was uneventful. He was born at term with birth weight of 4,000g. Contact was good. He could walk age 18 months and developed speech at 3 years. When he became older, there were behavioural problems with aggression. Present examination showed

height 175.5 cm (50th centile), weight 73.5 kg (75th to 90th centile), head circumference 55 cm (50th centile) and span 182 cm. The skin was very soft and there were striae on the upper limbs. His voice was hoarse, hypernasal and low pitched. Testes were normal. Stature was kyphotic.

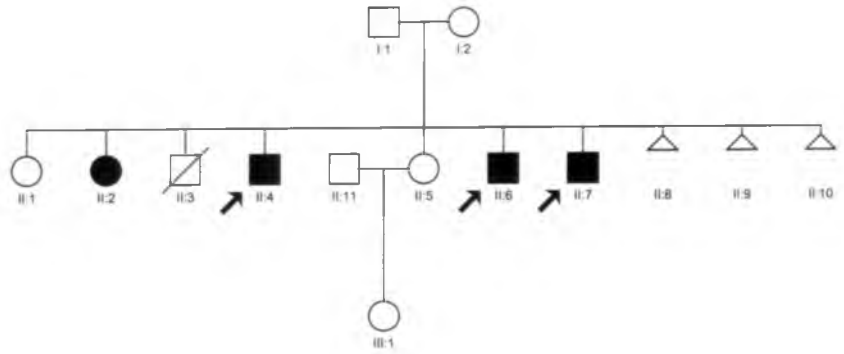

Figure 3
The family pedigree of the small MRX family with a non-sense mutation in the IL1RAPL gene. The three index patients are indiacted (II-4, II-6 and II-7)

2. Clinical description of the patient of the MRX44 family

This mildly mentally retarded male was the youngest boy of 5 children. He had an older moderately mentally retarded brother. The 2 other brothers and sister were normal. His mother had 2 mentally retarded brothers and her sister had 2 mentally retarded boys. Pregnancy was uneventful. He was born at term with birth weight of 3,160g. Postpartal, there were feeding problems. He could walk at age 16 months. He was hyperactive and he walked on the tips of his toes. Speech development started at age 2 years. He had severe sleeping problems and awakened often during the night. He had difficult behaviour with outbursts of aggression, with destroying objects and self mutilation. He was aggressive to other children and there were even periods of sexual aggression. Examination at the age of 30 years revealed height 172 cm (25-50th centile), weight 68.5 kg (75th centile), head circumference 59.4 cm (> 97th centile) and span 166.5 cm. There was synophrys, downward slanting palpebral fissures, lateral deviation of the nose, high nasal bridge and high arched palate. Cytogenetic studies revealed normal chromosomes 46,XY; no FMR1 expansion was found after molecular study, and linkage studies in this family showed a LOD score of 2.90 with marker DXS1204 in the region Xp11.3-p11.21 (17).

3. Non-specific familial mental retardation compatible with X linked inheritance (n=35)

Familial MR (first degree (n=63), second degree (n=6)) was present in 69 of the 215 males (32.1%) with idiopathic MR (Tables I and III). Of these 69 patients, pedigree data were not conclusive in 27 patients (39.1%). Paternal familial MR was present in 7 patients (10.1%). Maternal familial MR was present in 22 patients and 13 patients were members of affected sib pairs. X-linked inheritance was thus thought to be the most plausible mode of inheritance in 35 patients (50.7%) from 32 families. Three male sib pairs were living in the institution. In one of them

Table III Overview of the MR of the family members and their relation to the 69 mentally retarded males with non-specific familial MR

	Number	**Sib pairs living in this institution**
Not conclusive (n=27)		
Both parents affected	13	
Paternal familial MR (n=7)		
Affected father	2	
Affected father + several affected sibs	1	
Paternal familial MR	3	
Paternal familial MR + several affected sibs	1	
Maternal familial MR (n=22)		
Affected mother	5	
Affected mother + 1 or more affected sibs (brothers)	5	
Affected mother + 1 mildly affected sib (sister)	1	
Affected mother + 1 affected maternal brother	1	
Affected mother + 1 affected maternal sister and her affected child	1	
Affected maternal brother	5	
Affected maternal brother + 1 or more affected sibs (brother)	1	
Maternal familial MR + 1 affected sib (brother)	3	Including 1 sib pair (with severe neurological problems)
Affected brother pairs (n=13)		
1 or more affected sibs (brother)	12	Including 2 sib pairs
1 or more affected sibs (brothers) + affected child of sib (sister)	1	

spastic paraplegia was present in both. Of these 35 male patients 2 (5.7%) had microcephaly and both had dysmorphic features. Macrocephaly was present in 2 males (5.7%) and one had also macro-orchidism and dysmorphic features. Four males (11.4%) had micro-orchidism and 4 (11.4%) macro-orchidism as the only significant clinical finding.

DISCUSSION

Turner (29, 30) estimated that 20-25% of all mentally retarded males and possibly 10% of mild mental retardation in females is due to X-linked genetic defects (29, 30, 32). In this study of 436 adult mentally retarded males, living in a residential care system, we found that the proportion of males with XLMR was 13.1% (57/436) of the total male population or 24.1% (57/237) of the males without any other diagnosis. There were 16 males with fragile X syndrome, 2 with XLMR with marfanoid habitus, 4 with non-syndromic XLMR (MRX) and 35 with idiopathic MR and family history suggesting XLMR.

1.Syndromic XLMR (n=18)

1.Fragile X syndrome (n=16)

All 16 males were either moderately (62.5%) or severely (37.5%) mentally retarded. Clinical features in these adults were compatible with the typical Martin-Bell phenotype and one patient had also features of Prader-Willi syndrome. In the present group one third of the patients had epileptic seizures, which is high compared to the literature: seizures are observed in approximately 20% of young affected males, with a lower prevalence in adults, and in 5% of the females (9). In infancy, connective tissue abnormalities lead to congenital hip dislocations and inguinal hernia, and cause in later life scoliosis, flat feet, and mitral valve prolapse. In the present group there were 2 males with inguinal hernia and one with flat feet. Gastro-oesophageal reflux and tactile defensiveness lead to failure to thrive. One patient had problems of frequent vomiting in the neonatal period, although it was difficult to obtain reliable data of early development of most patients. Recurrent otitis media and sinusitis are present in 50% of cases and need adequate intervention to prevent complications. In the present group 3 had moderate hearing loss. In 30 to 50% of cases ophthalmologic help is needed because of strabismus (36%), myopia or hyperopia (22%) (9). In this group three older patients (18.8%) had severe loss of visual acuity, with strabismus in two. In the ageing fragile X patient, special attention should be given to detect early visual and hearing problems and therefore regular screening should be provided.

In general, fragile X patients are friendly, with attention deficit and hyperactivity in childhood, although some may show aggressive behaviour in adulthood (9). Behavioural problems in younger males include hand flapping, hand biting, tactile defensiveness, poor eye contact, hyperactivity, and perseverative speech while adults present autistic-like behaviour (10). In the present group, decrease of hyperactivity was noted. Special education and training is needed and speech therapists and physiotherapists can offer help in language and motor development.

2. X-linked MR with marfanoid habitus (MIM *309520) (n=2)

X-linked MR with marfanoid habitus was present in 2 moderately mentally retarded sporadic patients with ectomorphic habitus, triangular face, narrow palate, and hypernasal voice. Homocystinuria was excluded biochemically. Also Marfan syndrome was excluded since cardiac and ophthalmologic examinations were normal.

Several reports have been published on "X-linked mental retardation-marfanoid habitus syndrome" (11, 19, 25), including mild to moderate mental retardation, emotional instability, shyness, psychotic behaviour, marfanoid habitus with long hyperextensible fingers and toes, short halluces and long second toes (12). The marfanoid habitus becomes evident after puberty (13). Psychiatric problems include psychotic disturbances with hallucinatory visions and sounds (20), and schizophrenia (8, 26). However, the genetic defect remains to be discovered (21). The 2 present cases did not have a psychiatric history, only the first patient presented some autistic-like behaviour such as talking to himself, but both were very shy.

2. Non-specific X-linked mental retardation (MRX) (n=4)

Non-specific XLMR includes only mental retardation in affected persons without other dysmorphic features, neuromuscular symptoms, genital abnormalities, overgrowth, micro- or macrocephaly. Until recently, only the FMR2 gene, adjacent to the Fragile X-E (FRAXE) site on Xq28 has been identified as the cause of XLMR. Additional genes OPHN1 (oligophrenin 1) gene, PAK3 (p21 activating kinase), GDI1 gene, TM4SF2 gene, ARHGEF6 gene and RPS6KA3 gene have only recently been identified. A new gene, highly expressed in the brain, was isolated in the critical region Xp22.1-21.3 (4). A point mutation producing premature termination of the coding sequence was found in a small family with 3 sibs in this institution. The IL1RAPL1 gene encodes a 696 amino acid protein that has homology to IL-1 receptor accessory proteins and may be involved in memory

development and learning abilities. Non-overlapping deletions and a non-sense mutation in this gene were identified in patients with cognitive impairment only. The three brothers presented non-specific mental retardation without specific dysmorphic features. Speech was peculiar with hypernasality. Behavioural problems included self-mutilation and aggression.

The patient member of the MRX44 family, with normal clinical phenotype, presented periods of behavioural problems with self mutilation, aggression, destroying objects, and sexual aggression.

3. Patients with idiopathic MR and family history positive for XLMR (n=35)

In this group of 215 males with an idiopathic type of MR, non-specific familial MR (first and second relatives) was present in 32.1% (n=69). The presence of familial MR was three times increased in the maternal families (n=22) in contrast to the presence of MR in the paternal family (n=7). Also 13 patients were members of sib pairs. X-linked inheritance was thus considered in 35 males. In this group of 35 males, from 32 families, 5.7% were microcephalic with dysmorphic features and 5.7% were macrocephalic. Micro-orchidism and macro-orchidism were each present in 11.4%. Macrocephaly in association with macro-orchidism is an important finding in several X-linked mental retardation syndromes, including FRAXA (MIM* 309550), XLMR-macrocephaly-macro-orchidism (MIM 309530), XLMR-macrocephaly, Atkin-Flaitz syndrome, Clark-Baraitzer syndrome, Lujan-Fryns syndrome (MIM* 309520) and PPMX (Psychosis-Pyramidal signs-Macro-orchidism Syndrome (MIM300055)) (27). In the present group, only one patient had this association of macrocephaly and macro-orchidism together with dysmorphic features.

In general, the higher recurrence risk in brothers than in sisters strongly suggests that genes on the X chromosome are important contributing factors to the recurrence risk in undiagnosed mental retardation (31). X-linked inheritance was thus diagnosed in this institution in a group of 57 patients, accounting for 13.1% of the total male population (57/436), while in the group of males without any other diagnosis, this percentage was 24.1% (57/237). Regarding the general figure of XLMR in males (20 to 25%) a higher figure in this group of 436 mentally retarded males was expected. This indicates that also in the present survey several members of MRX families are currently not discovered. Since this is a population of older mentally retarded patients, family data are not always accurate and genetic counselling is not requested anymore. The influence of ageing and drug therapy, i.e. anti-epileptic drugs, may coarsen the face and hide the clinical diagnosis. In

addition, with advancing age, the natural history and medical complications are unknown.

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CHAPTER 3
METABOLIC DISORDERS

Content Chapter 3

3.1 METABOLIC STUDIES IN OLDER MENTALLY RETARDED PATIENTS: SIGNIFICANCE OF METABOLIC TESTING AND CORRELATION WITH THE CLINICAL PHENOTYPE

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ABSTRACT

In 471 adult mentally retarded adult patients (mean age 46 years; 92.6% males) living in an institution for the mentally retarded, a clinical examination, cytogenetic and molecular studies were done. 306 patients were screened for metabolic disorders. In 7 additional patients a metabolic disorder (phenylketonuria (n=5), mucopolysaccharidosis type III (Sanfilippo syndrome, type A) (n=1) and mucopolysaccharidosis type VII (Sly syndrome) (n=1)) was diagnosed in the past. The abnormal metabolic findings in this group of 313 patients were classified in three categories and the clinical findings are reported: 1. metabolic disorders as the cause of mental retardation (MR), 2. metabolic disorders not explaining the MR, and 3. metabolic abnormalities of unknown significance. The first two groups included 16 patients, i.e. 26.2% of the group of monogenic disorders and 3.4% of the total population: phenylketonuria (PKU) (n=5), S-sulfocysteinuria (n=3), mucopolysaccharidosis type III (Sanfilippo syndrome, type A) (n=1) and GM1-gangliosidosis type 3 (n=1) (first group), and mucopolysaccharidosis type VII (Sly syndrome) (n=1), Niemann-Pick syndrome, type B (n=1), cystinuria (n=1) and hyperprolinemia type 1 (n=3) (second group). The third group included patients with citrullinemia (n=2), methionine sulphoxide reductase deficiency (n=1), ornithinemia (n=1), glycinuria (n=20), neuraminaciduria (n=8), uraciluria (n=6) and diabetes mellitus (n=2). Screening for Congenital Disorders of Glycosylation (CDG) in 144 patients and for Smith-Lemli-Opitz syndrome (SLO) in a selected group of 6 patients was normal. Of the total group of 306 patients screened for inborn errors of metabolism, only 5 (1.6%) were found with a 'true' metabolic disorder. These 5 patients presented clinical symptoms, neurodegenerative or

behavioural problems, indicating further metabolic screening. The present study illustrates that a selected group of patients with mental retardation of unknown origin are candidates for metabolic screening, especially if aberrant behaviour, neurodegenerative problems or dysmorphic features are present.

INTRODUCTION

Few reports have been published on large-scale studies of inherited metabolic disorders. Yadav and Reavey (50) reported on 35 patients with aminoacidopathies in a group of 800 patients in Kuwait. Thirty-three of these 35 patients were the offspring of first-cousin consanguineous marriages. Carroll et al. (8) reported on sialic acid screening in neurologic disorders and Aula et al. (1) diagnosed 26 patients with aspartylglucosaminuria and 24 patients with Salla disease by screening urinary oligosaccharides in 1058 mentally retarded patients in Finland.

MATERIALS AND METHODS

During the systematic etiological survey in the institution of mentally retarded patients "Huize Assisie", Udenhout, The Netherlands, 471 patients (mean age 46 years; 92.6% males) were investigated and in 306 patients metabolic screening tests were performed. In 7 patients a metabolic disorder was diagnosed in the past and the clinical data of these patients were also included in the present study.

Patient records were studied and a written permission to perform a physical examination, to collect blood and urine for chromosomal studies on peripheral lymphocytes, and screening for inborn errors of metabolism, was obtained from the legal representatives. Molecular studies for the FMR-1 gene were done on specific indication. Family history and medical data were collected by questionnaire. All patients were tested by standard psychological methods to estimate their mental level. Urine and serum were obtained from these 306 patients. Because 24-hour urine collection is difficult to organise in mentally retarded patients, single urine and blood samples were obtained early in the morning. The blood sample was centrifuged at the institution and serum was transported to the Laboratory of Paediatrics and Neurology, University Medical Centre Nijmegen, The Netherlands. Screening on these samples was performed according to standard procedures, and included analysis of amino acids, organic acids, purines and pyrimidines, oligosaccharides, mucopolysaccharides and neuraminic acid. Six patients showed

MR, partial syndactyly of 2nd and 3rd ray of the feet and hypospadias, and they were screened for Smith-Lemli-Opitz syndrome (SLO) by measuring 7-dehydrocholesterol and cholesterol in serum. In 144 patients with idiopathic MR metabolic studies for Jaeken syndrome (Carbohydrate deficient glycoprotein or Congenital disorders of glycosylation (CDG syndrome)) were done by means of iso-electric focusing of plasma transferrin.

RESULTS

After a systematic etiological screening in 471 mentally retarded patients of this institution, 238 patients (238/471=50.5%) were found with an etiological diagnosis, including 61 with a monogenic disorder (44). Metabolic disorders were diagnosed in 16 patients i.e. 26.2% of the group of monogenic disorders and 3.4% of the total population. There was no consanguinity in the parents of these 16 patients.

In 7 patients a metabolic disorder was diagnosed in the past: PKU (n=5), Sanfilippo syndrome, type A (n=1), Sly syndrome (MPS type VII) (n=1). Of the 306 patients, screened for inborn errors of metabolism, 9 additional patients were diagnosed: an aminoacidopathy (Cystinuria (n=1), Hyperprolinemia (n=3), S-sulphocysteinuria (n=3)) was present in 7 patients and a lysosomal storage disorder in 2 patients (Niemann-Pick syndrome, type B (n=1), GM1 gangliosidosis type 3 (n=1)).

The clinical description and metabolic abnormalities in this group of patients are presented in tables I to VI, figures 1 and 2, and addendum 1.

Cholesterol and 7-dehydrocholesterol levels of the 6 patients screened for SLO syndrome, were in the normal range. In all 144 patients examined for CDG syndrome, normal plasma transferrin (iso-electric focusing of plasma transferrin) was found. Diabetes mellitus was diagnosed in 2 patients.

DISCUSSION

This study was an etiological study focused to detect the cause of the MR in this group of older mentally retarded patients. Therefore, the abnormal metabolic findings in this group of 306 screened and 7 previously diagnosed additional patients were further sub-classified in three categories: 1. metabolic disorders as the cause of mental retardation (MR), 2. metabolic disorders not explaining the MR, and 3. metabolic abnormalities of unknown significance.

Table I: Classification of all patients with metabolic disorders and metabolic abnormalities

Classification	Number of patients (n)
1. Metabolic disorders as the cause of MR	
Phenylketonuria (PKU) (MIM*261600)	5
S-sulphocysteinuria (MIM*272300)	3
Mucopolysaccharidosis type III (Sanfilippo syndrome, type A) (MIM*252900)	1
GM1 gangliosidosis type 3 (MIM#230650)	1
2. Metabolic disorders not explaining the MR	
Cystinuria (MIM#220100)	1
Hyperprolinemia type 1 (MIM*239500)	3
Mucopolysaccharidosis type VII (Sly syndrome) (MIM*253220)	1
Niemann-Pick syndrome, type B (MIM*257200)	1
3. Metabolic abnormalities of unknown significance	
Citrullinemia	2
Ornithinemia	1
Methionine-sulphoxide reductase deficiency	1
Glycinuria	20
Neuraminaciduria	8
Abnormal metabolites of lysosomal metabolism	4
Uraciluria	6
4. Diabetes mellitus	2

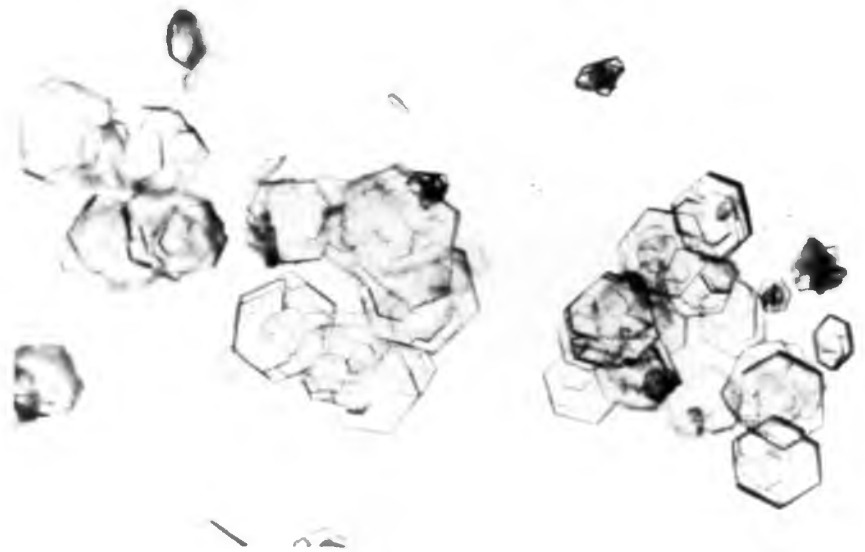

Figure 1
Cystine crystals in the urinary sediment of the profoundly mentally retarded male with cystinuria

Figure 2
Patient with GM1 gangliosidosis. Note the facial grimacing

Table II: Amino-acid metabolic disorders: clinical features of the patients with phenylketonuria, S-sulphocysteinuria, cystinuria and hyperprolinemia

Patient	Family	MR	Epilepsy	Neurology	Dysmorphism
Phenylketonuria (n=5)					
AA-1	Fam MR	Moderate	+	-	Light coloured hairs
AA-2	Fam MR	Profound	-	Motor problems turricephaly	Light coloured hairs Blue eyes
AA-3	Fam MR	Profound	+	-	-
AA-4	Fam MR	Profound	-	Motor problems	Coarse
AA-5	Fam MR	Profound	+	Microcephaly	-
S-sulphocysteinuria (n=3)					
AA-10	RFW (5-6)	Profound	+	Leucotomy Behaviour problems	Macrostomia, synophrys
AA-11	RFW (6)	Profound	+	Leucotomy Behaviour problems Microcephaly	Macrostomia Facial asymmetry
AA-12	-	Profound	+	Spastic tetraplegia Microcephaly	Macrostomia, Synophrys, Scoliosis Moderate vision loss
Cystinuria (n=1)					
AA-6	Fam MR	Profound	+	Self mutilation	-
Hyperprolinemia type 1 (n=3)					
AA-7	RFW	Mild	+	Aggressive Autistic-like	-
AA-8	RFW	Moderate	-	Microcephaly	SS
AA-9	RFW	Profound	+	Microcephaly	SS

RFW: recurrent fetal wastage (≥ 3 miscarriages); MR: mental retardation; SS: short stature; N: normal; R: right; +: present

Hearing loss	Biochemical Results			
-				
moderate				
severe				
-				
moderate				
	Urinary S-sulphocysteine concentration (normal value: <20 µmol/mmol creat)			
R ear: perforation	52 - 20 - 35			
Severe	34			
Severe	29 - 18			
	Urinary cystine (normal value: 6-34µmol/mmol creat)	Urinary lysine (normal value:7-58 µmol/mmol creat)	Urinary ornithine (normal value: 0-5 µmol/mmol creat)	Urinary arginine (normal value: 0-5 µmol/mmol creat)
-	390 - 339	787 - 764	335 - 323	235 - 230
	Urinary proline (0-9µmol/l)	Serum proline (83-391µmol/l)		
-	17 - 1	551 - 478 - 462		
moderate	2	524 - 546		
moderate	1	545 - 425		

Table III: Lysosomal metabolic disorders: clinical features

Patient	Diagnosis	MR	Epilepsy	Dysmorphism	Hearing loss	Neurology
LD-1	Sanfilippo syndrome, type A	Profound	+	Coarse face Hepatospleno-megaly	Severe	Progressive loss of motor function Behavioural problems
LD-2	GM1-ganglio-sidosis type 3	Mild	-	Long face, large ears, pectus excavatum	Mild	Progressive Hypotonia arms Hypertonia legs Facial dystonia
LD-3	Niemann-Pick syndrome, type B	Severe	-	Left-sided iris coloboma Left-sided haemangioma upper eye-lid Thin lips Splenomegaly	N	Dysarthric speech
LD-4	MPS type VII (Sly syndrome)	Moderate	+	SS	N	Normal Behavioural problems as child

+: present

1. Metabolic disorders as the cause of the MR

A. Aminoacidopathies

The 5 patients, members of 4 families, with PKU (Phenylketonuria (PKU) (MIM*261600)) were diagnosed after a systematic screening in 1967. In 2 families, there were other sibs with PKU and MR. The parents of the 2 brothers were borderline intelligent. Vogel (47, 48) observed an increased incidence of familial MR in PKU heterozygotes.

There were 3 patients with S-sulphocysteinuria (MIM*272300) and isolated sulphite oxidase deficiency (ISOD) was most likely (normal urinary xanthine and hypoxanthine, and uric acid levels). However, enzyme assay studies could not be performed. They had severe and difficult to treat epileptic seizures. There was recurrent fetal wastage with 5 to 6 miscarriages respectively in the parents of 2 patients. In ISOD, at the molybdenum cofactor centre, located in the intermembrane space of the mitochondrion, sulphite accumulates and sulphate production is decreased (5). S-sulphocysteine is formed by direct reaction of sulphite with cysteine and results in an increased urinary excretion of sulphite, thiosulphate,

Table IV: Clinical presentation of the patients with glycinuria

Patient	MR	E	Therapy	Clinical features	Familial	Hearing	Vision	Glycinuria (43-173 µmol/mmol creat)
Gly-1	Severe	+	Sodium valproate	Meningitis (meningococ)	3 RFW	Deaf	N	397 - 443
Gly-2	Severe	+	Carbamazepine Valproic acid Phenobarbital	Tremor Coordination abn Cerebellar abn Pyramidal abn	-	N	Mild	293 - 264
Gly-3	Moderate	+	Sodium valproate Carbamazepine Oxazepam	-	Fam MR	Mild	N	434 - 489
Gly-4	Severe	+	Sodium valproate Carbamazepine Phenobarbital	Asphyxia Microcephaly Dysmorphism Coarse face	-	Moderate	Mild	794 – 813
Gly-5	Severe	+	Carbamazepine Phenobarbital	Arachnoid cyst Microcephaly Dysmorphism Tetraplegia		N	Mild	500 - 367
Gly-6	Profound	+	Sodium valproate Carbamazepine Luminal	Tremor Ataxia	Fam MR	Mild	Mild	522 - 397
Gly-7	Mild	+	Sodium valproate	-	-	N	Moderate	296 - 235
Gly-8	Mild	+	Sodium valproate	BW:6,200g	Fam MR	N	N	592 – 409
Gly-9	Severe	+	Sodium valproate Carbamazepine	Macrocephaly Trichotillomania	-	Moderate	Blind	572 –274
Gly-10	Profound	+	Sodium valproate Carbamazepine	Microcephaly	4 RFW	-	-	317 – 389
Gly-11	Severe	+	Carbamazepine	-	-	Moderate	N	217 – 221
Gly-12	Moderate	+	Sodium valproate	Macrocephaly	-	N	N	Increased - 286
Gly-13	Moderate	-	Carbamazepine	Asphyxia Turricephaly Pyramidal abn Cardial abn	-	Moderate	N	418 – 338

Table IV continued

Patient	MR	E	Therapy	Clinical features	Familial	Hearing	Vision	Glycinuria (43-173 µmol/mmol creat)
Gly-14	Moderate	-	-	SS	Consan-guinity	N	N	265 –1336
Gly-15	Mild	-	-	Progressive neurological abn	Fam MR	N	N	211 – 241
Gly-16	Profound	-	Ranitidin	Asphyxia Pedes cavi Neurological abn No speech	Fam MR	Severe	N	Increased - 276
Gly-17	Moderate	-	-	Asphyxia Behavioural probl	-	N	Mild	292 - 576
Gly-18	Severe	-	Periciazine	-	Fam MR	N	N	316 - 266
Gly-19	Severe	-	Carbamazepine Dipiperon	Speech retardation	-	Mild	N	233 - 608
Gly-20	Moderate	-	-	Asphyxia Spasticity legs Pyramidal abn	-	Moderate	Mild	285 - 229

E: epilepsy; +: present; RFW: recurrent fetal wastage; N: normal; abn: abnormality; MR: mental retardation; BW: birth weight; SS: short stature; probl: problems

taurine and S-sulphocysteine. The severe neurological abnormalities, with poor prognosis, are a consequence of the neurotoxicity of sulphite accumulation or as a deficit in sulphate concentration. Barbot et al. (2) and van der Klei-van Moorsel et al. (45) described a mild type of ISOD with normal concentration of sulphate in urine, despite the complete absence of sulphite oxidase activity in fibroblasts. Probably, there is a relationship between the clinically milder form and the normal urinary concentration of sulphate. Garrett et al. (15) described a mutation in the sulphite oxidase gene in a 5 year-old girl with ISOD, who exhibited developmental delay, hypotonia, bilateral dislocation of the lenses and progressive neurologic abnormalities. An ophthalmological examination showed no lens dislocation in the third patient, but he had moderate loss of visual acuity. He had also severe non-progressive spastic paraplegia.

B. Disorders of lysosomal metabolism

The patient with Sanfilippo syndrome, type A (Mucopolysaccharidosis type III; MPSIIIA) was diagnosed at age 10 months because of psychomotor retardation and hepatosplenomegaly. At age 10 years, he had severe behavioural problems with self

Table V: Clinical presentation of the patients with neuraminaciduria

Patient	Neuraminaciduria Biochemical results (5-65 µmol/mmol creat)	Medication	MR	Epilepsy	Neurology	Dysmorphism	Hearing loss
NA-1	85	-	Mild	-	Autistic-like psychotic behaviour	Macrocephaly Normal phenotype	N
NA-2	79	Carbamazepine Phenobarbital	Profound	+(severe)	Frontal leucotomia Pica	Coarse	N
NA-3	87	-	Severe	+	Bil pes cavus Autistic	Normal phenotype	N
NA-4	73	Cisordinol Akineton	Severe	+	Self mutilation	Microcephaly Microphtalmia	Severe
NA-5	71	Carbamazepine Lioresal Melleril	Severe	+	Myopathy		Mild
NA-6	75	-	Moderate	-	Motor irritability	Microcephaly SS	Severe
NA-7	88	Carbamazepine	Severe	+	Frontal leucotomia Aggressive	Normal phenotype	Mild
NA-8 =Gly-4	140	Sodium valproate Carbamazepine Phenobarbital	Severe	+		Microcephaly Coarse: large mandible, hypertelorism Myopia Barrel-shaped chest	Moderate

MR: mental retardation; +: present

mutilation and sleep difficulties. The clinical features in MPSIIIA include severe central nervous system degeneration with delayed development, coarse hair, hirsutism, diarrhoea, mild skeletal abnormalities, joint stiffness, and hepatosplenomegaly in older patients. Behavioural problems with destructive tendencies and hyperactivity are frequent presenting symptoms (32).

The patient diagnosed with GM1 gangliosidosis type 3 (beta-galactosidase deficiency) presented since the age of 7 years progressive neurologic deterioration with dysarthria, progressive gait disturbance, and dystonia in the neck and extremities. Brain imaging showed only periventricular atrophy. Uyama et al. (42)

Table VI: Clinical presentation of the patients with uraciluria

Patient (years)	MR	E	Medication	Neurology	Dysmorphism	Biochemistry uraciluria (0 – 5 mmol/mol creat)
U-1 (48 y)	Profound	+	Carbamazepine Dipiperon	Polyneuropathy	Coarse: synophrys, deep-set eyes, broad nasal tip Coarse ears SS	30.9 – 36
U-2 (51 y)	Severe	-	-	Self mutilation	Microcephaly Low frontal hairline	16 – 22
U-3 (18 y)	Severe	-	Neuleptil	Pica Self mutilation Autistic Progressive loss of speech	Synophrys, flat midface Scoliosis	24.7 – 23.9
U-4 (26 y)	Severe	-	-	Anxious Irritability	Down slanting palpebral fissures, synophrys	57.4 – 39.2
U-5 (62 y)	Moderate	+	-	Dystonia Dysarthria Spasticity Atrophia m deltoideus	Severe perceptive hearing loss	30.9 – increased
U-6 (50 y)	Severe	+	Phenobarbital		Moderate hearing loss	53 – 30.3

E: epilepsy; +: present; SS: short stature; m: musculus

reported MRI lesions in the putamen and nucleus caudatus, which may be responsible for the symptomatic dystonia which is characteristic of this disorder. Age of onset of the first neurological symptoms may be variable (4 to 30 years) (39, 49, 41). Additional symptoms are mild mental retardation, epileptic seizures, angiokeratomas of the skin, and mild spondylodysplasia with flattened vertebral bodies, but organomegaly and cherry red spots are no typical findings (40).

2. Metabolic disorders not explaining the MR

A. Aminoacidopathies

In one profoundly mentally retarded male, cystinuria (MIM#220100) was present. Cystine, lysine, ornithine and arginine levels were all highly increased. He was considered as a type 1 cystinuria patient, although it was not possible to determine the carrier status of the family members. Two profoundly mentally retarded brothers died at early age. In cystinuria there are 3 clinical types and the

genetic defect (2p16.3 (SLC3A1 gene)) results in a defective heavy subunit of the renal aminoacid transporter (rBAT), with defective cystine transport in the brush border of the proximal renal tubule and the intestinal epithelium. This results in defective reabsorption of cystine and dibasic aminoacids, most probably by means of a heteroexchange diffusion mechanism of transport with neutral aminoacids (7, 28, 29, 34). Interestingly, Scriver et al. (33) observed a 10 fold increased incidence of cystinuria in mentally retarded patients. However, the possibility of a contiguous gene syndrome exists. Also 'hidden' consanguinity may be an explanation of this increased incidence of MR.

There were 3 patients with hyperprolinemia type 1 (MIM*239500). One was mildly, one moderately, and one profoundly mentally retarded. In addition, 2 of the 3 patients had short stature, microcephaly, and moderate hearing loss, and 2 of the 3 had epileptic seizures. In the 3 families there was recurrent fetal wastage. Hyperprolinemia type 1 is a very rare disorder and is generally considered as a benign condition, although EEG abnormalities, photogenic epilepsy, nerve deafness, and mental retardation have been reported. The defect involves the enzyme proline oxidase in the degradation pathway of proline, a non-essential amino acid important in connective tissue collagen and in the brain as a precursor of the GABA neurotransmitter (26, 27).

B. Disorders of lysosomal metabolism

The patient with MPS Type VII (Sly) presented moderate mental retardation, severe epileptic seizures, short stature and behavioural problems. The diagnosis was also confirmed (beta-glucuronidase deficiency) in 2 other institutionalised mentally retarded sisters. The clinical presentation of Sly syndrome is heterogeneous and clinical features include coarse face, corneal opacities, hearing loss, hepatosplenomegaly, pectus carinatum, skeletal defects with abnormalities of the vertebral bodies (35). Lee et al. (23) differentiated a severe early-onset type and a mild late-onset type. Urinary MPS (chondroitin sulphate) excretion, variable with age, was observed by Lee et al. (23) in one patient. Intelligence is normal or may be impaired (11, 38).

The patient with Niemann-Pick syndrome, type B presented a normal phenotype but splenomegaly was found after abdominal ultrasound investigation. He had left-sided iris coloboma. In Niemann-Pick syndrome sphingomyelinase deficiency (11p15.4-p15.1) results in storage of sphingomyelin in reticuloendothelial cells and ganglion cells. Several subtypes are described. However, only type A (classic type) and B (visceral type) are caused by sphingomyelinase deficiency. Type B manifests

with organomegaly without neurological abnormalities. Type B patients express an enzyme with sufficient residual activity to prevent neurologic manifestations. Splenomegaly may not be noted until adulthood (3, 24, 31). Intelligence is normal. However, Sogawa et al. (37) reported 2 males with mental retardation and hepatosplenomegaly.

3. Metabolic abnormalities of unknown significance

In 42 patients biochemical disturbances of unknown significance or secondary to drug therapy were found. Of these patients, 24 had abnormal values of urinary and/or serum amino acids.

Citrullinemia was present in 2 patients. Both patients had behavioural problems with self mutilation. One patient had familial MR and parents were consanguineous (second cousins). MR was present from early childhood. In adult-onset citrullinemia (type II citrullinemia) (CTLN2) (7q21.3) (MIM#603471), mental retardation, bizar behaviour, sleep reversal, echolalia, tremor, convulsions, psychosis, manic periods and hallucinations are present (6, 21, 22, 30). In the urea cycle argininosuccinate synthetase (ASS), catalyzes the formation of argininosuccinate from citrulline and aspartate (30). It was difficult to conclude whether the repeatedly abnormal findings in the present two patients with aberrant behaviour indicated a metabolic disorder or were caused by exogenous food suppletion.

An increased serum level of ornithine was found in one patient. Two inherited disorders result in hyperornithinemia. Gyrate atrophy of the choroid and retina, with symptoms limited mainly to the eye is caused by a deficiency of the mitochondrial matrix enzyme ornithine aminotransferase (OAT) (MIM*258870). Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, with symptoms resulting from ammonia accumulation and protein aversion, results from a defect in the transporter that mediates ornithine entry into mitochondria (MIM#238970) (43). A disorder of the urea cycle was excluded in the present patient.

The clinical significance of methionine-sulphoxide reductase deficiency in the patient with 45,X/46,XY/47,XYY mosaicism and testis tumor was not clear. Methionine levels in this patient were normal. Whether the increased plasma and urinary methionine-sulphoxide levels were caused by the presence of the testis tumor or whether this patient presented a new metabolic disorder could not be resolved, because he died before additional studies were performed. Metabolic studies in patients with a similar gonadal tumor type were started. Recently, Huang et al. (20) reported on changes in methionine adenosyltransferase deficiency (MAT) which seem to be important in the pathogenesis of hepatocarcinogenesis.

Methionine and methionine-sulphoxide are increased in hepatic MAT deficiency (MIM*250850), which is usually considered a clinically benign condition which may present clinically with breath odor (12, 13, 16, 19, 25).

Glycinuria was present in 20 patients, and in 19 patients glycine concentration in serum was normal. Treatment with anti-epileptics, especially depakine, is an explanation for the increased urinary glycine in 14 patients. Two patients were treated with neuroleptic drugs. In 4 other patients it was difficult to explain the glycinuria. Until the age of 6 months physiological iminoglycinuria is a common finding. Persistent glycinuria has been reported in association with aminoaciduria in hyperprolinemia and hydroxyprolinemia, in Fanconi syndrome and in renal glycinuria as a specific error of membrane transport of aminoacids. Renal glycinuria should be differentiated from dominantly inherited renal hyperglycinuria, autosomal dominant glucoglycinuria, and X-linked hypophosphatemia with glucoglycinuria. Familial iminoglycinuria is a benign condition involving nonessential amino acids, and no therapy is indicated. (9, 17). In conclusion, glycinuria without hyperglycinaemia is probably a benign condition without clinical symptoms.

Abnormal results of lysosomal metabolism were found in 12 patients. Neuraminaciduria was present in 8 patients, including 6 with severe behavioural problems. The family of the sialic acids is derived from neuraminic acid and the predominant sialic acid in humans is N-acetylneuraminic acid (sialic acid). Although intralysosomal accumulation of free sialic acid has been documented in several organs, its role is unknown (14). Salla disease and infantile free sialic acid storage disease (ISSD) are probably allelic mutations of a gene coding for a lysosome membrane transport protein (36). The clinical findings in Salla disease include hypotonia, ataxia, nystagmus, spasticity, delayed psychomotor development, and impaired speech development, EEG abnormalities, and coarse face. In ISSD failure to thrive, visceromegaly, edema and early death are characteristic findings (14). In sialuria, with accumulation of free sialic acid in cytosol and not in the intralysosomal fraction, developmental delay, hepatosplenomegaly and coarse facial features are the clinical findings. However, definite conclusions concerning the diagnosis of a metabolic disorder could not be made in these 8 patients.

In 4 patients, abnormalities of metabolites of the lysosomal metabolism were present and the significance of these abnormal levels was not clear. In one patient this was probably due to medication.

Biochemical abnormalities in the purine and pyrimidine metabolism were found in 6 patients with uraciluria, but no clear diagnosis could be made and the significance was not known. Pyrimidines play an important role in the regulation

of the central nervous system and metabolic changes affecting the levels of pyrimidines may lead to abnormal neurological activity. Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the degradation of the pyrimidine bases. DPD deficiency is often accompanied by a neurological disorder with a wide variety in clinical presentation (46). Large concentrations of thymine and uracil are detected in urine, blood and cerebrospinal fluid. Uraciluria may indicate the presence of hyperammonemia. In 2 patients postprandial ammonia was measured and was normal.

CONCLUSION

Bradley (4) suggested screening on amino acids, mucopolysaccharides and mellituria in every infant with failure to thrive, mental retardation or neurological defect. Guidelines to perform metabolic screening, concerning mitochondrial cytopathies, peroxisomopathies, and inborn errors of neurotransmission, were reported by Haan (18). Recently, Curry et al. (10) published recommendations on evaluation of mental retardation, and concluded that metabolic testing should be selective and targeted at patients with symptoms suggesting this category of disorders and that unselected metabolic screening should not be routinely performed in patients with MR. In the present study, only 5 additional patients were found with a metabolic disorder and 4 patients with a metabolic disorder without clear relation with mental handicap. The diagnosis of other metabolic disorders besides PKU (systematic screening of newborns) and the clinically recognisable lysosomal storage disorders remains low in institutionalised mentally retarded persons. Screening for the CDG syndrome was done for the first time on a large scale of patients since the biochemical procedure became available for routine procedures. However, no patient was diagnosed with CDG syndrome. In 6 selected patients, based on the presence of MR, partial syndactyly of the 2nd and 3rd toes and hypospadias, cholesterol and 7-dehydrocholesterol were measured, but the diagnosis of SLO was not confirmed. These data suggest that the number of patients with these syndromes among institutionalised mentally retarded may be not as high as previously thought. Therefore, we agree with Curry et al. (10) to perform only basic metabolic screening in a selected group of mentally retarded patients in whom chromosomal studies, microdeletion studies and DNA studies appeared normal. Patients with the diagnosis of "birth complication" and the presence of behavioural abnormalities, neurodegenerative problems or dysmorphic features are the first candidates for selective metabolic screening.

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ADDENDUM 1: METABOLIC ABNORMALITIES OF UNKNOWN SIGNIFICANCE: PATIENT DATA AND CLINICAL DESCRIPTION

1. Biochemical abnormalities in amino acid metabolism (n=24)

1. Citrullinemia (n=2)

Two patients were found with increased serum citrulline. The first patient was a 61 years old moderately mentally retarded male and family history revealed 2 miscarriages. Behaviour was bizar and autistic-like and there was aggression, self mutilation, echolalia and echopraxia, stereotypias, facial dystonia. Renal function was normal. There was partial syndactyly of the second and third toes. Citrullinemia was present: 73 and 74 μmol/l (normal value: 23-49 μmol/l) .

The second patient was a 69 years old profoundly mentally retarded male. Parents were consanguineous. He had one profoundly mentally retarded brother, who had normal biochemical levels of citrulline. Craniofacial features included brachycephaly, coarse face with hypertelorism, large mouth, high arched palate and there was deafness. There was self mutilation and he was very anxious. Renal function was normal. Citrullinemia was present: 79 and 72 μmol/l.

2. Ornithinemia (n=1)

A 59 years-old severely mentally retarded patient had an increased serum ornithine level (141 and 142μmol/l (normal value: 29-103μmol/l). He had one mentally retarded sister. There were no dysmorphic features, he had only strabismus convergens. There was no speech and behaviour was normal. To exclude a disorder of the urea-cycle, serum ammonia was measured after protein-rich diet and was found to be normal.

3. Methionine-sulphoxide reductase deficiency (n=1)

Basic metabolic studies in a 55 years old moderately mentally retarded male revealed an increased plasma and urinary methionine-sulphoxide level. The patient's karyotype was 45,X/46,XY/47,XYY (6/43/1). There was no familial history of mental retardation. Psychomotor development was delayed. Span was 10 cm above height and OFC was on the 3rd centile. He had no dysmorphic features. There was a partial cutaneous syndactyly of the second and third toes. Methionine-sulphoxide was repeatedly increased in plasma (91 and 308 μmol/l) and urine (40 and 60 μmol/mmol creatinine). Unfortunately, before complementary studies could start, the patient died, because of complications of status epilepticus and respiratory insufficiency after metastatic testis cancer. Postmortem studies revealed a malignant gonadal stromal tumor.

4. Glycinuria (n=20)

In 20 patients (Table IV) an increased value was found of the urinary glycine excretion and varied between the level of 211 and 1336 µmol/mmol creatinin (normal value: 43-173 µmol/mmol creatinin). Fourteen patients received anti-epileptic therapy. One patient received periciazine (Neuleptil) and one patient ranitidine. There was no oral therapy in 4 patients. Patient Gly-15 had also increased serum glycine of 501 and 443 µmol/l (normal value: 154-358 µmol/l). Cerebrospinal fluid was not investigated. He suffered from an unknown progressive neurologic disorder. He had 2 mentally retarded children. Patient Gly-14 had first degree consanguineous parents.

2. Biochemical abnormalities in lysosomal metabolism (n=12)

1. Neuraminaciduria (Table V) (n=8)

Eight patients presented an increased level of urinary neuraminic acid. Six of these 8 patients showed severe behavioural problems and 2 of them were surgically treated in the past with a frontal leucotomy.

2. Other unknown abnormalities of lysosomal metabolism (n=4)

Screening for lysosomal disorders was also disturbed in 1 profoundly mentally retarded patient (Patient AA-11)(Table II). Epileptic seizures, microcephaly, mild craniofacial dysmorphism, deafness, loss of visual acuity were present. Psychomotor development was retarded and he was surgically treated because of severe behavioural problems of self mutilation. Amino acid screening showed an increased value of glycine and S-sulfocysteine. However, enzyme assay studies on mucopolysaccharidoses in leucocytes were normal.

Screening for lysosomal disorders in another profoundly mentally retarded patient showed an unknown urinary metabolite. Contractures, epileptic seizures, hypertelorism, large ears, high palate and pectus excavatum were present. Visual acuity was severely decreased. Cytogenetic studies and DNA investigation for the FMR-1 gene were normal. Enzymatic studies in leucocytes on mucopolysaccharidoses revealed no abnormalities.

In 1 patient heparansulfate was increased, but enzyme studies on mucopolysaccharidoses showed normal values. He was profoundly mentally retarded, epileptic seizures and progressive neurologic deterioration was present. There was macrocephaly, coarse face, palatoschizis and he was blind. There was severe hearing loss. A cerebral CT-scan showed a large right sided parieto-occipital porencephalic cyste. A definite metabolic diagnosis could not be made.

In 1 mildly mentally retarded patient disturbances of oligosaccharide excretion

was present probably due to medication treatment of his psychotic behaviour (Fluanxol, Nozinan and Orpenadrine).

3. Biochemical abnormalities of purine and pyrimidine metabolism (n=6)

Uraciluria was present in 6 patients (Table VI). Postprandial ammonia was measured in the patients U-2 and U-3 and was normal. Patient U-1 was mentally retarded and presented dysmorphic features. Patient U-4 presented dysmorphic features of mild Cornelia de Lange syndrome and patient U-5 had distinct neurological symptoms with atrophy of shoulder muscles and facial dystonia.

CHAPTER 4
DYSMORPHOLOGY AND MENTAL RETARDATION

Content Chapter 4

4.1 Description of Patients with Dysmorphic Syndromes

4.1.1 Zimmermann-Laband Syndrome in a Patient with Severe Mental Retardation

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Abstract

The Zimmermann-Laband syndrome (ZLS) is a rare autosomal dominant disorder characterized by gingival hyperplasia or fibromatosis, various skeletal anomalies including dysplasia of the distal phalanges of thumbs and halluces, vertebral defects, and hepatosplenomegaly. Thus far, 23 cases, including 11 patients from 2 families, have been reported. Most cases of ZLS have a normal intelligence although some cases are mildly retarded. Differential diagnosis includes other causes of gingival hyperplasia.

We report on a patient with ZLS and severe mental retardation and review the literature.

We conclude that severe mental retardation is a feature of the syndrome.

Introduction

The Zimmermann-Laband syndrome is a rare autosomal dominant disorder characterized by gingival hyperplasia or fibromatosis, various skeletal anomalies including dysplasia of the distal phalanges of the halluces and thumbs, vertebral defects, and hepatosplenomegaly. The first two patients were described by Zimmermann (15). Most patients reported have a normal intelligence. There are a few patients with a borderline intelligence and one patient with severe mental retardation. We report on another patient with severe mental retardation and review the literature.

CASE REPORT

The proband, a 54 year-old male, was severely mentally retarded. He was the fourth child of healthy non-consanguineous parents. He had 3 healthy siblings. At birth, his father was 38 years old and his mother 36 years old. There was no family history of either mental retardation or ZLS. Birth weight was 4.5 kg (>97th centile). The absence of thumb- and halluxnails was noticed. He showed mental retardation at the age of 2 years. Because of seizures anti-epileptic therapy with phenobarbital and diphantoin was started at age 7 years. Multiple root remnants and fibromata of the upper jaw were surgically removed at age 53 years.

Clinical examination showed a wheel-chair bound male with a heigth of 165 cm (3rd-10th centile) and a weight of 51 kg (3rd centile). Head circumference was 57 cm (50th-97th centile). Craniofacial features included a coarse face with poor expression, a full fleshy nose, hypoplasia of zygoma and maxilla, downslanting palpebral fissures, ptosis (L>R), strabismus divergens, retrognathia, a flat philtrum, a high narrow palate, absence of teeth and gingiva hyperplasia (Fig. 1, 2). Hair implantation on the skull was thin with bushy eyebrows, but hair structure and distribution on the rest of the body were normal. Because of tonic-clonic seizures, carbamazepine was prescribed. Hearing was normal. Truncal obesity was present; there was no hepatosplenomegaly. He had scoliosis and paresis of both legs with contractures of the hips and right knee. Thumbnails were absent but the other fingernails were normal (Fig. 3). Phalangeal joints were hyperextensible. Feet were short with absent halluxnails and hypoplastic toenails (Fig. 4). The Vineland Adaptive Behavior Scale showed severe psychomotor retardation.

Figures 1 & 2
Facial appearance and profile of the patient

Figure 3
Left hand, not the absent thumbnail.

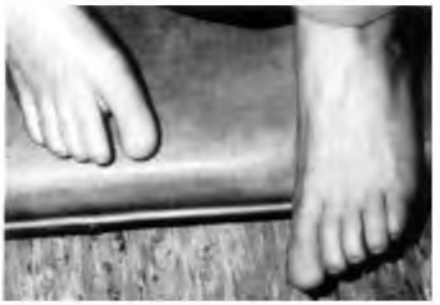

Figure 4
Hypoplatic toenails and absent halluxnails

TECHNICAL INVESTIGATIONS

Radiologic investigation of hands and feet showed subluxation of both thumbs with short, broad distal phalanges. Distal phalanges of second and fifth fingers of both hands were hypoplastic (Fig. 5). Halluces were short, broad and hypoplastic and distal phalanges of the other toes were also hypoplastic (Fig. 6).

Cytogenetic investigation showed a normal male karyogram: 46,XY (Fragile X negative). Screening for inborn errors of metabolism was normal.

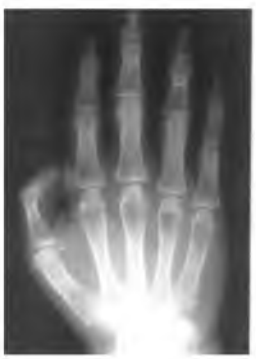

Figure 5
X-ray of the right hand, note subluxation of the thumb and the short, broad distal phalanges and the hypoplastic distal phalanges of the second and fifth fingers

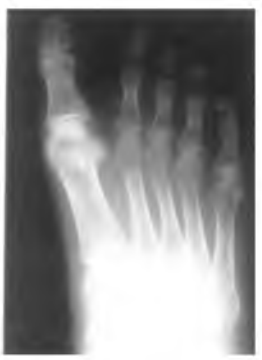

Figure 6
X-ray of the right foot, note the short, broad and hypoplastic hallux and the hypoplastic distal phalanges of the other toes

DISCUSSION

The diagnosis of ZLS in our patient was based on the typical clinical findings: coarse face with full fleshy nose, high narrow palate, gingival hyperplasia, scoliosis, dysplasia of the distal phalanges of thumbs and halluces with absent thumbnails and halluxnails and hypoplastic toenails.

Differential diagnosis includes other causes of gingival hyperplasia which are shown in Table I and the DOOR syndrome (deafness-onycho-osteo-dystrophy-retardation) (5, 6, 14). Although anti-epileptic therapy can cause gingival

Table I: Differential diagnosis of gingival hyperplasia (GH)

A. With other abnormalities			
Name	**Birth defects MIM**	**Major manifestations**	**Inheritance**
Cowden Syndrome	0412 *158350	GH-hypertrichosis fibroadenomas of breasts	AD
GH-hypertrichosis	0410 135400	GH+hypertrichosis	AD
Jones Syndrome	2315 *135550	GH-sensorineural hearing loss	AD
Rutherfurd Syndrome	0408 *180900	GH-corneal dystrophy	AD
Zimmermann-Laband	0409 *135500	GH-digital anomalies	AD
Cross Syndrome	0413 *257800	GH-athetosis-depigmentation microphtalmia	AR
Puretic Syndrome	0411 *228600	GH-multiple hyaline fibromas Murray syndrome	AR
Ramon Syndrome	2610 266270	GH-cherubism-seizures hypertrichosis	AR
B. Without other abnormalities Autosomal dominant Autosomal recessive Exogenous (drugs eg. phenytoin, cyclosporin A) Unknown			

hyperplasia, it does not explain the other features in our patient. Unfortunately, we do not know whether gingival hyperplasia was present before anti-epileptic therapy was started. Mental retardation and epilepsy are common components of syndromes associated with gingival fibromatosis. These other syndromes are clearly different from the patient reported here. The diagnosis of DOOR syndrome was rejected because of the absence of sensorineural hearing loss and characteristic facial dysmorphism in our patient.

Twenty-three cases of Zimmermann-Laband syndrome (10 males and 13 females) have been reported. In Table II, the main clinical features of ZLS are summarized. Of 3 patients, only data on the presence of gingival hyperplasia and aplasia of the nails were available (cases 15, 16 and 17). Included are 2 families with autosomal dominant inheritance. In one family, a mother, her 2 sons and 3 daughters were affected (11). In the second family, a mother, her 3 sons and 1 grandson had ZLS (1). The 12 other patients were sporadic cases and were probably a result of a new mutation. Of the 23 cases with ZLS, 5 patients were mildly mentally retarded (cases 2, 4, 18, 21 and 22) and 1 patient had a mildly delayed motor development (case 23). Chodirker et al. (7), described one patient with "ZLS and profound mental retardation" (case 19). This patient was also the only other patient with epilepsy and anti-epileptic therapy. To our knowledge, our patient is the second case of ZLS with severe mental retardation. We conclude that severe mental retardation is a feature of the syndrome. Although the two patients with severe mental retardation were sporadic cases, more cases should be reported to evaluate the relevance of this finding for genetic counseling of patients and families with ZLS. Heterogeneity in an autosomal recessive syndrome or variable expression may be possible explanations but the most probable explanation, however, is a contiguous gene syndrome in ZLS.

ACKNOWLEDGEMENTS

We thank Professor R.J. Gorlin, MD, for expert advice and B. De Witte, MD, for his help in interpreting the X-rays.

Table II: Zimmermann-Laband: Main clinical features

Case	Reference	Sex	Age	Mental Retardation	GH	Facial features*	Hepato-spleno-megaly	Nails[1]	Hands[2]	Feet[3]	Vertebral defects
1	Zimmermann (15)	M	16y	-	+	5	-	+	+	+	+ (spina bif.occ.)
2	Zimmermann (15)	F	10y	mild	+	1;3;4	-	+	ND	ND	-
3	Jacoby et al. (10)	F	2,5y	-	+	2	-	+	+	+[4]	+ (spina bif. occ.)
4	Laband et al. (11)	F	38y	low level	+	1;2	+	-	+	-	-
5	Laband et al. (11)	M	14y	-	+	1;2	+	+	+	-	-
6	Laband et al. (11)	F	13y	-	+	1;2	+ hepatom.	+	+	-	-
7	Laband et al. (11)	M	12y	-	+	1;2	+ splenom.	+	+	-	+ kyphosis
8	Laband et al. (11)	F	8y	-	+	1;2	+	+	+	-	-
9	Laband et al. (11)	F	5y	-	+	1;2	-	+	+	-	-
10	Alavandar (1)	F	59y	-	+	1;2	-	+	+	+	-
11	Alavandar (1)	M	29y	-	+	1;2	-	-	+	+	-
12	Alavandar (1)	M	23y	-	+	1;2	+	-	+	+	-
13	Alavandar (1)	M	16y	-	+	1;2	+ hepatom.	-	+	+	-
14	Alavandar (1)	M	9 mth	-	+[5]	-	-	-	+	+	-
15	Atanasov et al. (2)	F?	16y	ND	+	ND	ND	+	ND	ND	ND
16	Atanasov et al. (2)	M?	23y	ND	+	ND	ND	+	ND	ND	ND
17	Atanasov et al. (2)	M?	65y	ND	+	ND	ND	+	ND	ND	ND
18	Oikawa et al. (13)	F	ND	mild	+	1;2;4;5	+ hepatom.	+	+	+	+ kyphosis
19	Chodirker et al. (7)	M	30y	profound	+	1;2;3;4	-	+	-	-[4]	+ scoliosis
20	Beemer (4)	F	20y	-	+	1;3;4	-	+	+	+	-

Table II continued

Case	Reference	Sex	Age	Mental Retardation	GH	Facial features*	Hepato-splenomegaly	Nails[1]	Hands[2]	Feet[3]	Vertebral defects
21	de Pino Neto et al. (8)	F	8y	mild	+	1;2;3	+	+	-[6]	+[4]	-
22	Bazopoulou et al. (3)	F	8y	mild	+	1;3;5	-	+	+	+	-
23	Lacombe et al. (12)	F	8 mth	mild?[7]	+	1;2;4;5	+ hepatom.	+	+	+	ND
24	Present report	M	54y	severe	+	1;2;5	-	+	+[6]	+[4]	+ scoliosis

*Facial features: 1: bulbous soft nose; 2: thick floppy ears; 3: large tongue; 4: thick lips; 5: full eyebrows

[1]Nails: aplasia or dysplasia; [2]Hands: distal phalanges absent or dysplastic; [3]Feet: distal phalanges absent or dysplastic; [4]abnormal shape distal phalanx of the hallux; [5]thickened epithelium on the alveolus; [6]abnormal shape distal phalanx of the thumb; [7]motor development was mildly delayed

ND: No Data; - : not present; + : present; GH: Gingival hyperplasia; Hepatom.: Hepatomegaly; Splenom.: Splenomegaly; Spina bif. occ.: Spina bifida occulta

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4.1.2 FOUNTAIN SYNDROME: FURTHER DELINEATION OF THE CLINICAL SYNDROME AND FOLLOW-UP DATA

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ABSTRACT

We present five patients with the clinical diagnosis of Fountain's syndrome, an autosomal recessive entity with mental retardation, deafness, skeletal abnormalities and coarse face with full lips as cardinal features and review all cases reported so far. We report two new isolated cases, and present follow-up data on three previously reported patients. The clinical features of all these patients are presented to further delineate the clinical picture and the natural course of this rare syndrome. We propose that epilepsy, short stature, large head circumference, broad, plump hands and the remarkable behavior are important accessory findings of this syndrome. The clinical features of this syndrome become more evident with advancing age.

INTRODUCTION

Fountain (1) described in 1974 a family with four members with a specific clinical picture including mental retardation, deafness, skin granulomata, and bone abnormalities. Fryns et al. (2, 3) reported 3 moderately to severely mentally retarded males (2 brothers and 1 sporadic male patient) with congenital deafness due to an inner ear anomaly, facial plethorism and skeletal anomalies. We describe two new isolated patients and present follow up studies of the three patients described by Fryns et al. (3) to delineate the clinical picture and the natural course of this syndrome.

CASE REPORTS

Patient 1

The patient, (AA), now 50-years-old and institutionalized from the age of 10 years, was a moderately mentally retarded male. He was the first child of healthy, non-consanguineous parents. The second pregnancy ended in a stillborn girl. His only brother was healthy but had severe perceptive hearing loss. Pregnancy was uneventful. He was born at term. Birth weight was 3,250 g (25th centile). Psychomotor development was delayed. He could sit at the age of 3 years, walked at 4 years and developed speech at 5 years (Figure 1A). At age 10 years, he weighed 26 kg (10th-25th centile) with height of 118 cm (7 cm < 3rd centile) and head circumference of 52 cm (25th centile). Clinical investigation showed abdominal obesity, lumbosacral lordosis, thick skin, undescended right testis, hypotonia of the upper and lower extremities, and a large, curved tongue. His total psychological score was 4 years 5 months. At age 19 years, severe vision loss due to high grade myopia was diagnosed and corrected with vision aids. When he was 27 years, he weighed 53 kg (1 kg < 10th centile) with height of 158 cm (4 cm < 3rd centile) and headcircumference of 58 cm (97th centile). He had severe vision problems, high and small palate, absent right testis, and weak motor development of both legs. Age 36, severe bilateral hearing loss was confirmed with a loss of 50 to 70 dB on the right and 65 to 80 dB on the left ear. He suffered since one year from chronic otitis media. Two years later, myopia gravis was found at the left eye with an ulcer of the cornea and glaucoma of the right eye for which he was treated with laser therapy. At age 44 he was helped with a hearing device at the left ear. Recently, he became totally blind. He suffered from chronic infections of the upper respiratory tract.

Present investigation showed a very friendly, well nourished, short statured male with a height of 159 cm (3 cm < 3rd centile) and weight of 67.5 kg (50th-75th centile). He had a turricephalic skull with a head circumference of 59.5 cm (0.5 cm > 97th centile) and sparse hair implantation. He had a coarse face with thick eyebrows, downward slanting palpebral fissures, blindness and a chronic conjunctivitis of the left eye (Figure 1B). His ears were asymmetrical, with a rather simple structure and hair on the helices, and measured 7 cm (75th to 97th centile) (right ear) and 7.5 cm (97th centile) (left ear). He had a flat midface, large mandible and large open mouth with thick full lips and high palate. The skin of the cheeks was very soft. There was truncal obesity, hypotonia of the abdominal muscles, and small testes. Bilateral cubitus valgus was noticed. The hands were broad and large with a total hand length of 20 cm (>97th centile) and relatively short fingers. On the right hand there was a simian crease. X-rays of hands, skull and spine showed

Figure 1A & B
Aggravation of the facial coaseness and full lips in patient 1

general osteoporosis, plump aspect of the hands with tufting of the distal phalanges, and sclerosis of the skull base and plathyspondyly. Chromosomal analysis on a peripheral blood lymphocyte culture showed a normal 46,XY male karyotype. DNA studies were performed to exclude the fragile-X syndrome. The result of an extensive screening for inborn errors of metabolism was normal and excluded mannosidosis and aspartylglycosaminuria.

Patient 2

This boy, R.d.J., was the second child born to healthy, nonconsanguineous parents. The family history was negative for mental retardation. His mother was 22 and his father 25-years-old at the time of his birth. He was born after an uneventful pregnancy and delivery at gestational age of 40 weeks, with a birth weight of 3,100g (10th-25th centile). An omphalocoele was detected at birth and surgically corrected on the first postnatal day. The neonatal period was complicated by a sepsis and bacterial arthritis of the left hip resulting in necrosis of the femur head. There were neonatal feeding problems and recurrent infections. The boy was able to walk with support at age 18 months and without support at age two and a half years (Figure 2A). There was an extreme delay in language development and deafness was suspected. At age 4 years sensorineural deafness was confirmed by electrocochleography: no response was detectable below 2 kHz. At age 5 years nocturnal epileptic attacks developed, that worsened with advancing age (Figure 2B). Seizures were of generalized tonic-clonic type. Interictal EEG's were normal until age 16 years. After that age a slowing of the background activity appeared to correlate with mental regression and increase of seizures during the day. Cerebral CT scans at age 13 and 16 years were normal. At age 11 years bilateral

orchidopexia was performed.

Physical examination at age 17 years showed a moderately mentally retarded boy with length of 175 cm (25th centile) and head circumference of 55.5 cm (50th centile). He had an extremely friendly and optimistic behavior. There was brachycephaly with broad forehead. Mild hypertelorism, with ICD of 3,5 cm (75th to 97th centile) and OCD of 10,2 cm (97th centile), and ptosis of the eyelids were seen (Figure 2C). The ears were slightly posteriorly rotated and ear pits were bilaterally present. The nose was large with bulbous tip (septum and alae nasi). The mouth was large with full lower lip. The palate was extremely high and narrow with hyperplasia of the gums. There was no oligodontia. Retrognathia and broad neck were noticed. There was acne. Scoliosis was present and was ascribed to a post-infectious shortening of the left femur. Hand length was 18 cm (50th centile), the palms of the hands were short with palm length of 9,5 cm (10th centile), and the fingers were stubby.

Figure 2A, B & C
Aggravation of the facial coarseness and full lips patient 2

Chromosomal and ophthalmological investigations revealed no abnormalities. Screening for inborn errors of metabolism was normal and excluded mannosidosis and glycosaminuria. In the cerebrospinal fluid (CSF) there was a slight increase of neuron specific enolase (15.7µg/l; Normal: 1.6-14.5 µg/l) and of S-100 (7;1 µg/l; Normal 0.9-5.5 µg/l) compatible respectively with neuronal and glial damage. No HbH bodies were detectable in peripheral blood. Cerebral MRI scan at the age of 17 years showed T2W signal increase in semi-ovale centers bilaterally and normal subcortical U-fiber myelinisation. An X-ray of the skull showed sclerosis of the

basis of the skull. X-rays of the hands confirmed the plump aspect of the hands, tufting was within the normal ranges. The skeletal age was 15 years at chronological age of 17 years.

Patient 3

The patient, PV, now 43-years-old, was the first child of healthy unrelated parents. His sister was normal and had two normal boys. His brother (patient 4) was mentally retarded and deaf. These two brothers were reported by Fryns et al. in 1987 (3). PV was born after an uneventful pregnancy at term with birth weight of 4,150 g (90th centile). At age 3 months, he developed hypsarrhythmia with seizures which were difficult to control despite ACTH therapy. Later he developed grand mal epilepsy and focal seizures of the left arm. Deafness was noted at age 15 months. Clinical investigation at age 29 years showed a mildly retarded male with height of 170 cm (25th centile), weight of 62 kg (25th-50th centile) and a head circumference of 55 cm (25th-50th centile). He had a peculiar round and coarse face and with mild swellings of the subcutaneous tissue of the lips and cheeks. His hands and feet were short and broad with short and broad terminal phalanges. Ophthalmological, biochemical and metabolic investigations were normal. Cytogenetic investigation, including G- and R-banding, showed normal male karyotype 46,XY. Profound sensorineural hearing loss with rudimentary hearing at the lowest frequencies was noted on audiometry; the vestibular function of the ear was normal. The pars petrosa of the temporal bones showed anomalies on the cochlea on X-ray tomography. X-ray of the skull showed thickness of the calvaria and X-rays of the hands and feet confirmed the broad and plump aspect of the hands and feet. Since a few years he worked in a sheltered workshop, before he worked as a butcher. At age 42 years he was hospitalized several times because of severe epileptic attacks.

Present investigation showed a mildly mentally retarded male in good general condition. His length was 170 cm (25th-50th centile), weight of 65 kg (50th-75th centile) and head circumference of 58.6 cm (97th centile). He had severe hearing loss and there was no speech, but he could communicate by using hand movements. He had a very friendly personality. He had long and coarse face, with high forehead and flat midface. There was synophrys and OCD was 10.5 cm (>97th centile) and ICD 3.3 cm (75th-97th centile). Lips were full and everted, the skin of the cheeks was soft with loose subcutaneous tissue (Figure 3A). Hands were broad and plump with total hand length of 19.5 cm (97th centile) and palm length of 11.5 cm (75th-97th centile).

Patient 4

This patient, LV, was the younger brother of patient 3. He was a 36 years old and severely mentally retarded. Pregnancy was uneventful. Birth weight was 3,900 g (75th-90th centile). At age 3 months he developed infantile spasms which later resulted in generalized convulsions. Psychomotor development was moderately to severely retarded. He could walk at 18 months of age. Profound hearing loss was diagnosed at that time. Since the age of 5 years he was institutionalized. At age 18 years, he showed mental regression. Physical investigation at 26 years showed a severely mentally retarded male with height of 172 cm (25th-50th centile), weight of 65.5 kg (50th-75th centile) and head circumference of 55.5 cm (50th centile). He had long coarse face with open mouth and full everted lips, high palate, small teeth, and mandibular prognatism. The swelling of the subcutaneous facial tissues, especially of the lower lip, became more evident between 13-26 years of age. He had generalized hypotonia and thoracolumbar scoliosis. Hands and feet were broad and plump. Screening for inborn errors of metabolism was negative. Chromosomal investigation showed normal male 46,XY karyotype. Audiometry showed severe sensorineural hearing loss with normal vestibular function. X-ray investigation of hands and feet showed thickened corticalis without ossification anomalies. X-ray of the skull showed marked thickness of calvaria. Tomography of the pars petrosa of the left temporal bone showed a congenital anomaly of the left inner ear. The cochlea was replaced by a simple cavity. Ophthalmological investigation was normal.

Figure 3A & B
Facial appearance of the 2 brothers at the present age of 43 years in patient 3 (A) and 36 years in patient 4 (B)

Present investigation showed a severely mentally retarded male with height of 172 cm (25th-50th centile) and weight of 65.5 kg (50th-75th centile). He had no speech, but he could communicate by using simple hand movements. He had an extreme friendly behavior. He looked microcephalic, although his head circumference was 55.5 cm (50th centile). His face was long and coarse, with flat midface and long forehead. There was pro-optosis with OCD of 11.5 cm (>97th centile) and ICD of 2.8 cm (25th-50th centile). He had extreme full everted lips, high palate, and coarse nose (Figure 3B). Pectus excavatum, lumbar scoliosis, and hypotonia of the abdominal muscles were noted. Hands were broad with lower implantation of the thumbs, and he had flatfeet.

Patient 5

The patient, W.V.L., a 26-year-old severely mentally retarded male, was the second born of three children. His two sisters were normal. There was no consanguinity and both parents were in good health. Pregnancy was uneventful. Birth weight was 2,750 g (25th-50th centile) at 36 weeks. Psychomotor development was severely delayed. When he was 2 years old, a round, plethoric face and short stubby hands and feet were noted. At age 4 years, he was severely retarded and could not walk or speak. His height was 93 cm (3rd centile), weight 15.2 kg (25th centile) and head circumference 51.5 cm (50th-75th centile). The diagnosis of complete bilateral sensorineural deafness was made at this age. He was institutionalized at age 6 years. Physical investigation at 17 years of age (see Fryns et al. (3)) revealed severe mental retardation, deafness, edemateous coarse face with thick everted lips, full cheeks, and depressed nasal bridge. Hands and feet were short and plump and X-ray confirmed the presence of broad, heavy phalanges and metacarpals with thick cortices but whithout ossification defect. Length was 143.5 cm (<3rd centile). He had severe motor impairment and could hardly walk without support. Screening for inborn errors of metabolism was normal and chromosomal investigation showed normal male karyotype: 46,XY.

Present investigation showed a severely mentally retarded male with height 163 cm (1cm > 3rd centile), weight 67.5 kg (50th-75th centile) and head circumference 58.5 cm (97th centile). The span was 167.5 cm. His behavior was very friendly. There was no speech. He had coarse face with normal midface and large mandible. There was acne. He had small eyelashes with epicanthus (Figure 4A). He had full lips and the lower lip was everted. Hairline was low and the nose was very coarse (Figure 4B). Thorax was barrelshaped and there was abdominal obesity. There was bilateral camptodactyly of 5th fingers. He walked atactic and the musles of the lower extremities were hypoplastic.

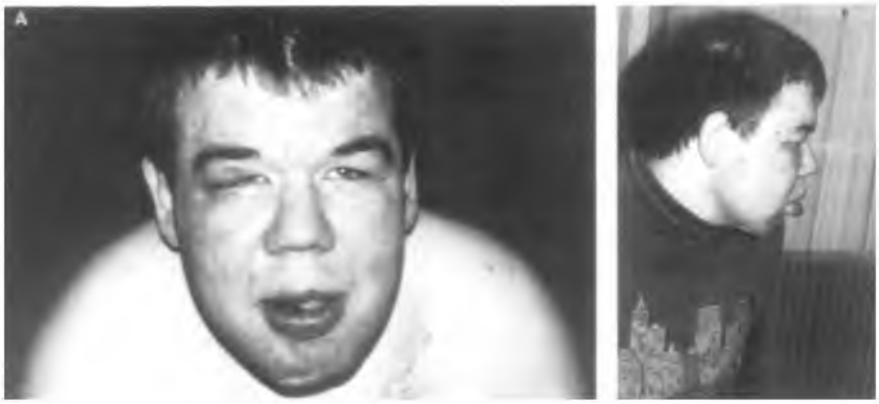

Figure 4A & B
Facial appearance of patient 5 at the age of 26 years

DISCUSSION

Mental retardation, deaf mutism and skeletal abnormalities were first reported by Fountain in 1974 (1), in a family with 4 affected sibs. The two oldest children, a girl and a boy, had also gross papular swelling of the skin of the cheeks, upper lip and chin. The fourth child died and had spina bifida. X-rays of the skull of the 3 oldest children showed thickened calvarium. The mental retardation and deafness became more clear at age 2-3 years.

Patients 3,4 and 5 of this report were first published by Fryns et al. in 1987 (3). Follow-up data of these three patients are presented in this report. The abnormal facial appearance in all three patients became more evident. Patient 3 suffered from severe epileptic attacks, for which hospitalisation was neccesary during the last years. Due to change in therapy his clinical condition improved. His brother (patient 4) and patient 5 did well and had no specific health problems.

Of the two new patients with Fountain syndrome, described in the present report, patient 1 was a moderately mentally retarded patient and he was the only patient in his family. However, his brother had a severe hearing loss and was helped with hearing aids but he was not mentally retarded and had a normal phenotype. Patient 2 had delayed psychomotor development and he had severe epileptic insults. He was also the only patient in his family. Table I gives an overview of all reported and present cases.

Of the five present patients there were three patients with epilepsy (cases 2, 3 and 4), three with rather large headcircumference (cases 1, 3 and 5), two with

thoracal abnormalities (cases 4 and 5) and two with scoliosis (cases 2 and 4). All patients had coarse face, mental retardation, deafness and broad plump hands. Small stature is noticed in two patients (cases 1 and 5) and was also noted in the first patient of Fountain (girl) (1). Patient 1 had also severe myopia leading to blindness. An omphalocoele, which was corrected the first postnatal day was noted in patient 2. Noteworthy is the remarkable behavior of all patients who were extremely friendly.

Differential diagnosis includes Coffin-Lowry syndrome, alpha-thallassemia syndrome and Melkersson-Rosenthal syndrome. Coffin-Lowry syndrome is characterized by hypoplastic appearance of the distal phalanges and dysplasia of the vertebral bodies. In alpha-thalassemia syndrome, hearing is normal and inclusions of hemoglobin in red blood cells are observed. Melkersson-Rosenthal syndrome is an autosomal dominant disorder without mental retardation and without deafness; and swellings of the gums, cheeks, and lips can be seen. Fountain (1) wrote in a subscript of his publication that "a substance, probably aspartylglycosaminuria, has now been isolated", but further data were lacking. In our patients aspartylglycosaminuria was excluded.

Considering all the patients that have been reported up to now, we conclude that the mode of inheritance in Fountain syndrome is most likely autosomal recessive. Follow-up studies showed that the parents of the sibs, reported by Fountain, came from the same part of London (1). In the two brothers, reported by Fryns et al. (2, 3), X-linked inheritance is possible, although there were no other patients in their family. The other three patients were sporadic cases.

The clinical signs in the two new described patients matched well with the previous reported ones (2). We propose that epilepsy, short stature, large head circumference, broad and plump hands and the friendly behavior are accessory features of this syndrome. Follow-up data suggest that the clinical picture becomes more clear with advancing age with extreme coarsening of the face and severe hearing impairment. The follow-up data of cases 2 and 4 suggest possible slow decline in mental functioning, which is associated in patient 2 with CSF changes compatible with cerebral degeneration. Follow-up in patient 3 showed an evolution to difficult to treat epilepsy.

Table I: Features in the Fountain syndrome : review

Reference	**Fountain (1)**	**Fountain (1)**	**Fountain (1)**	**Fountain (1)**	**Present case 1**
Age (yrs)	22	24	21	ND	50
Sex	F	M	M	ND	M
MR	+	+ (IQ75)	+	+	moderate
Epilepsy	ND	ND	ND	ND	-
Deafness	+	+	+	ND	+
OFC	ND	ND	ND	ND	59.5cm (>P97)
Face	coarse	coarse	ND	ND	coarse
Midface	ND	ND	ND	ND	flat
Eyes	ND	ND	ND	ND	blind/thick eyebrows
Lip/cheek	full/swelling	full/swelling	normal	ND	full/swelling
Length	150cm (1cm<P3)	ND	ND	ND	159cm (3cm<P3)
Thorax	normal	ND	ND	ND	normal
Hands	ND	ND	ND	ND	broad/relative short fingers
Feet	ND	ND	ND	ND	normal
Behavior	ND	ND	ND	ND	friendly
X-ray skull	thickening calvarium	thickening calvarium	thickening calvarium	ND	ND
Other	gingival hypertrophia			spina bifida	high palate

ND = no data, M = Male, F = Female, MR = Mental retardation, + = feature is present, - = feature is not present, P = centile

Present case 2	**Present case 3 (Fryns et al. (3))**	**Present case 4 (Fryns et al. (3))**	**Present case 5 (Fryns et al. (3))**
17	43	36	26
M	M	M	M
moderate	mild	moderate	severe
+	+	+	-
+	+ sensorineural	+ sensorineural	+
55.5cm (P50)	58.6cm (P97)	55.5cm (P50)	58.5cm (P97)
coarse	coarse/long	coarse/long	coarse
normal	flat	flat	normal
ptosis/hypertelorism	synophrys	pro-optosis	small eyelashes/ epicanthus
full	full/swelling	full/swelling	full/swelling
175cm (P25)	170cm (P25-P50)	172cm (P25-P50)	163cm (P3)
normal	normal	pectus excavatum	barrel shaped
stubby/short hands	broad/short terminal phalanges	broad/plump	short/plump
normal	normal	normal	short
friendly	friendly	friendly	friendly
normal MRI: increased signal	thickening calvarium	thickening calvarium	ND
ear pits large nose hyperplasia gums scoliosis omphalocoele		coarse nose scoliosis	coarse nose, large mandible atactic walk

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4.1.3 Björnstad Syndrome in a Patient With Mental Retardation

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Abstract

Pili torti or twisted hair can appear as an isolated defect, in association with other ectodermal defects, in association with other clinical features or can be acquired. Björnstad syndrome is a rare condition with apparent autosomal recessive inheritance, characterized by hearing loss and twisted hairs (pili torti). All patients with Björnstad syndrome reported thusfar have normal intelligence. We report on a patient with severe mental retardation and review the literature.

Introduction

Anomalies of the hair are a main feature in several developmental defects. Pili torti or twisted hair can appear as an isolated defect, in association with other ectodermal defects, in association with other clinical features or can be acquired.

Björnstad syndrome is a rare condition characterized by sensorineural hearing loss and twisted hairs (pili torti) (1). Additional reports have been published (2, 6-10). All patients with Björnstad syndrome reported thusfar have normal intelligence. We report on a patient with pili torti, hearing loss and severe mental retardation and review the literature.

Case Report

The index patient of this report is a 57-years-old severely mentally retarded male. He was the 6th child of healthy non-consanguineous parents. His 8 brothers and sisters are healthy and also their children. Pregnancy and birth were uneventful.

Psychomotor development was retarded from the beginning. There was no speech development. At the age of 7 years he was hospitalized because of a disorder affecting the skin of the skull. No further information was available about this disorder, except that he received radiation therapy only. At the age of 52 years, severe sensorineural hearing loss of 70 dB on the left side and of 50 dB on the right side was diagnosed. He learned some signs of non-verbal communication. He had visual agnosia and therefore he suffered from apraxia.

Present investigation showed a severely mentally retarded male, with a length of 175.5 cm (50th centile), weight of 60.1 kg (25th to 50th centile) and head circumference of 58.1 cm (97th centile). He had a long face. The posterior hairline was high (Fig. 1). The hair of the skull was sparse and brittle. The eyebrows and eyelashes were sparse. The skin, nails and teeth were normal. There was thoracic hyperkyphosis. Speech was absent and communication was poor. He had a bilateral pes cavus deformity. Walking was clumsy. He showed a normal behaviour, although he was anxious during the examination.

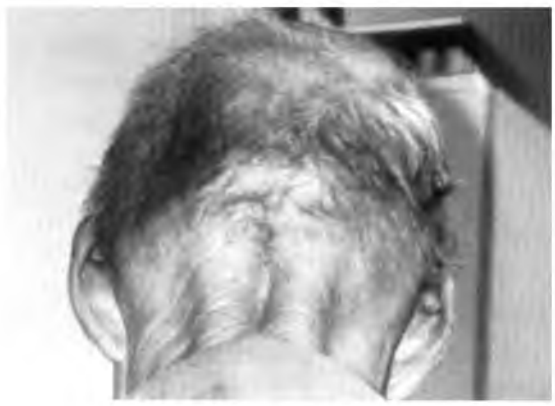

Figure 1
Note the brittle hair and the high posterior hairline

TECHNICAL INVESTIGATIONS

Cytogenetic investigation showed a 46,XY normal male karyotype and molecular study of the FMR-1 gene was normal. Screening for inborn errors of metabolism was normal. Scanning electron microscopy of the hairs of the skull revealed severely abnormal hairs with flattening, grooving, twisting, pili torti, and sometimes with the aspect of a pilum triangulatum (Figs. 2 and 3).

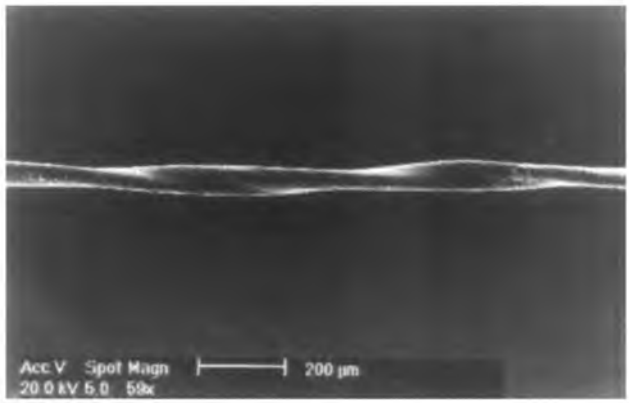

Figure 2
Scanning electron microscopy shows twisting and flattening of the hairs

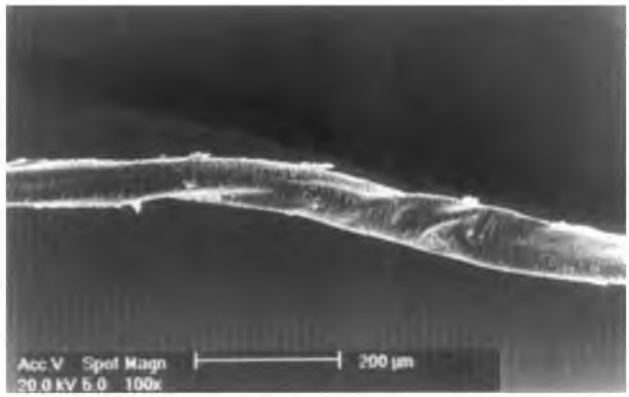

Figure 3
Grooving of the hairs of the skull

Discussion

The diagnosis of Björnstad syndrome in our patient was based on the association of severe hearing loss and the abnormalities of the hair. There were no other clinical features of ectodermal dysplasia. A cause for his severe mental retardation could not be found. Speech was absent, probably as a consequence of his hearing deficit, diagnosed at the age of 52 years only.

Pili torti can appear as an isolated defect or can be found in association with

other ectodermal abnormalities (9). Acquired pili torti after trauma was excluded in our patient, because there was no history of self mutilation. Differential diagnosis included other syndromes with pili torti. In Menkes kinky hair syndrome, an X-linked disorder, affected males show growth retardation, cerebral and cerebellar degeneration, hair abnormalities with trichorrhexis nodosa and have low copper and ceruloplasmin serum levels (5). Monilethrix, pseudomonilethrix and argininosuccinic aciduria were also excluded in our patient, as none of these syndromes is associated with hearing loss (4, 9). Also the syndrome of hyperkeratosis palmoplantaris striata - pili torti - hypodontia - sensorineural hearing loss described by Egelund and Frentz in a 14 years old female is a different clinical condition (3).

In Björnstad syndrome, the main clinical features are sensorineural hearing loss in association with pili torti: Björnstad (1965) (1) reported on eight individuals with pili torti and five had also sensorineural hearing loss. Two of these five patients had affected siblings and one an affected aunt; the two other patients were isolated cases. The patients with the most pronounced hair anomalies had the most severe hearing problems. The scalp hair, eyebrows and eyelashes were affected (1). Reed et al. (1967) (7) reported on 4 additional patients: 3 siblings and one patient whose mother was probably affected, but who was not examined. He equally noted that the patients with the most severe hair problems also showed severe hearing loss (7, 8). Voigtländer (1979) (10) reported one family with 2 affected siblings and concluded that the syndrome is probably inherited as an autosomal recessive condition. Robinson and Johnson (1967) described a female with severe hearing loss and pili torti (8). Two new families and a restudy of a third family were presented by Cremers and Geerts (1979) (2). These authors hypothesized that pili torti is an autosomal dominant disorder with low penetrance of a pleiotropic manifestation of hearing loss. Two non-related children with pili torti were reported by Scott et al. (1983) (9). One of them had sensorineural hearing loss. Their family history was negative for hair abnormalities. Petit et al. (1993) (6) reported on 3 patients in 1 family, a mother with two affected children, and equally suggested an autosomal dominant inheritance.

In conclusion, the main clinical feature in all patients with Björnstad syndrome is pili torti of the hairs of the skull. Eyelashes and eyebrows are not always affected. Also, sensorineural hearing loss is not seen in all patients. Therefore, hearing should be tested in patients with pili torti in order to offer early treatment and hearing devices, certainly in young children with developmental delay.

ACKNOWLEDGEMENTS

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4.2 MOLECULAR CYTOGENETIC STUDIES IN DYSMORPHIC MENTALLY RETARDED PATIENTS

4.2.1 DYSMORPHOLOGY AND MENTAL RETARDATION: MOLECULAR CYTOGENETIC STUDIES IN DYSMORPHIC MENTALLY RETARDED PATIENTS

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ABSTRACT

In an institutionalised population of 471 mentally retarded adult residents (436 males and 35 females), 18 patients (16 males and 2 females) with dysmorphic features were selected to perform FISH studies by using subtelomeric probes to discover cryptic terminal deletions or duplications, undetectable with standard banding techniques. In the 13 investigated patients, no abnormalities were found with a selected battery of subtelomeric probes. The results of cryptic chromosomal rearrangement studies are variable but the frequency of positive diagnostic findings seems to be lower than previously expected.

INTRODUCTION

Until recently, chromosomal studies were performed according to standard procedures and included analysis of 15-20 GTG banded metaphases on peripheral blood lymphocyte cultures (18). At present, new molecular cytogenetic techniques are available (fluorescence in situ hybridisation techniques (FISH)) (6) and are used to confirm the clinical diagnosis of a number of well known contiguous gene syndromes such as Shprintzen syndrome (velo-cardio-facial syndrome (22q11 deletion syndrome), Williams-Beuren syndrome (7q11 deletion syndrome; elastin gene), Miller-Dieker syndrome (17p13.3); Wolf-Hirschhorn syndrome (4p deletion syndrome) and Cri du chat syndrome (5p deletion syndrome). In addition, small

deletions/duplications, which are not detectable with standard cytogenetic techniques, can be discovered by using this method. Also small (familial) translocation rearrangements (cryptic translocations) can be found in families with apparently normal chromosomes (11, 14).

Method of the Study

In the present study, out of 471 mentally retarded residents (mean age: 46 years; 436 males and 35 females) of the Institution for the mentally retarded Huize Assisië, Udenhout, The Netherlands, 18 patients with dysmorphic features, without clear diagnosis, or with a clinical diagnosis were selected. After an extensive study of their clinical file accomplished with a clinical examination and routine chromosomal investigation, DNA-studies to exclude the FMR-1 gene mutation and/or Angelman syndrome, and screening for metabolic disorders, FISH studies were done, by using subtelomeric probes to discover cryptic terminal deletions or duplications, undetectable with standard banding techniques. A selected battery of subtelomeric probes was used, according to the clinical features in each patient (Nijmegen checklist: unpublished data). Table I gives an overview of mental level, clinical features and selected panel of subtelomeric probes in each patient. The subtelomeric probes used in this study have been described previously (10, 11, 13).

Results

In 2 patients (patients 2 and 8) a syndrome diagnosis was made based on the clinical features of the patients. Only 13 patients could be investigated, since 3 patients moved to another institution, one patient died and one patient was not investigated (Table I). Until now, no abnormalities were found in this selected group of patients (Table I).

Discussion

In the present study of 13 mentally retarded adults, selected on the basis of their clinical phenotype and family histories, no cryptic chromosomal deletions/duplications were detected with a selected battery of subtelomeric probes, up to 7 individually adapted probes per case. The patients were selected by the

Table I: Summary of the clinical features and selected panel of subtelomeric probes in each patient

Number Sex	Age (years)	Pedigree data	Mental level	Dysmorphic features	Selected panel of subtelomeric probes
1. Female	33	No familial MR	Borderline	Cleft palate-divergent strabism-sacral dimple	2q,4q,8p,10p,13q, 18p
2. Male	50	No familial MR	Mild	Weaver syndrome-macrocephaly-hypertelorism-small mouth-small genitalia	1p,5q,8p,11q,16p, 22q
3. Male	46	No familial MR	Moderate	flat occiput-epicanthal folds-hypertelorism-large ears-prenatal growth retardation	1p,8p,11q,22q
4. Male	46	No familial MR	Moderate	long face- frontal upsweep-hypertelorism-large ears-pedes cavi-hearing problems	1p,8q,10q,18q,22q
5. Male	47	Familial MR: both parents and other sibs	Moderate	macrocephaly-frontal bossing-downward slanting palpebral fissures-hypertelorism-hearing loss-epicanthal folds-strabismus-high palate-bifid uvula-small genitalia-nystagmus	1q,6q,7p,9q,16q,22q
6. Male	24	Familial MR: paternal sibs	Severe	macrocephaly-downward slanting palpebral fissures-hypertelorism-epicanthal folds-ptosis-bifid uvula-hearing loss-corpus callosum agenesis-cryptorchidism	1p,6p,7p,9q,10p,22q
7. Male	43	No familial MR	Severe	Clinical features of Angelman syndrome-strabismus	1p,1q,6p,7p,18q,22q
8. Male	50	Familial MR: 3 sibs (2 females) and maternal family	Severe	Mild Cornelia de Lange-prenatal growth retardation-large hypoplastic ears	1p,7p,16p,18q,22q
9. Female	13	No familial MR	Severe	cleft palate-facial asymmetry- broad helices-hypertelorism-SS-scoliosis-spasticity	1p,6p,7p,10p,18q, 21q,22q

Table I continued

10. Male	50	No familial MR	Profound	E-coarse face-synophrys-strabismus-hypertelorism-large ears-SS-macroorchidism	1p,6p,7p,10q,18q, 22q
11. Male	49	No familial MR	Profound	Macrocephaly-strabismus-large mandible-downward slanting palpebral fissures-pectus excavatum-microorchidism	1p,7p,9q,22q
12. Male	36	Familial MR: son of maternal sister	Profound	Clinical features of Angelman syndrome-microcephaly-prenatal growth retardation	1p,1q,7p,10p,10q, 22q
13. Male	51	No familial MR	Profound	hair abnormalities-facial dysmorphism-cutis verticis gyrata-thick helices	1p,5q,16q,18p,22q

MR: mental retardation
SS: short stature
E: epileptic seizures

clinical geneticists of the Department of Human Genetics, University Medical Centre St Radboud, Nijmegen, The Netherlands. A panel of subtelomeric probes was selected according to the Nijmegen checklist (unpublished data). Prenatal growth retardation and a positive familial history for mental retardation, in addition to phenotypic features suggesting a chromosomal abnormality may indicate the presence of subtelomeric rearrangements (4). Knight and Flint (9) observed facial dysmorphism, minor physical abnormalities of the hands and feet, small stature, and microcephaly as consistent findings in patients with moderate or severe mental handicap, in combination with a small chromosomal anomaly.

Table II presents an overview of the results of previous studies of subtelomeric chromosomal rearrangements in selected groups of patients with idiopathic mental retardation or non-specific MR/MCA syndromes.

Slavotinek et al. (14) reported on 27 patients with MR/MCA and there were 2 patients in whom a small subtelomeric deletion was discovered. Knight et al. (11) reported their search for submicroscopic subtelomeric rearrangements and deletions in a population of 466 children (284 children with moderate to severe mental retardation and 182 children with mild mental retardation) with idiopathic mental retardation. Subtle rearrangements were found in 7.4% of moderately to severely mentally retarded patients and in 0.5% of the children with mild mental retardation. Half of these rearrangements were familial cases with cryptic balanced reciprocal

translocations resulting in unbalanced derivate chromosomes in the affected family members. In these affected individuals no consistent phenotype was present and often the diagnosis of "birth injury" was made in the past. Furthermore, they concluded that cryptic chromosomal rearrangements are the most frequent chromosomal disorder after Down syndrome, and they advised use of subtelomeric probes to screen all individuals with unexplained moderate to severe mental retardation. Joyce et al. (8) (2 abnormal findings in 93 patients) and Lamb et al. (12) (1 abnormal finding in 43 patients) found much lower frequencies (2.2%-2.3%). Finally, Turner and Partington (15) tested 20 patients with idiopathic mental retardation with an incomplete battery of subtelomeric probes, but they found no positive cases, as was also experienced in the present study. In the Leuven experience, only 1 patient out of 60 (1.6%), selected on familial mental retardation or mental retardation with dysmorphic features, was detected with a cryptic chromosomal rearrangement (unpublished data).

Table II: Overview of previous studies on subtelomeric rearrangements

Study	**Total number of patients**	**Frequency (%)**	**Clinical information**
Flint et al. (6)	99	6%	Idiopathic MR
Giraudeau et al. (7)	99	7.4%	Idiopathic MR
Slavotinek et al. (14)	27	7.5%	Moderate to severe idiopathic MR
Knight et al. (11)	284	7.4%	Moderate to severe idiopathic MR
Knight et al. (11)	182	0.5%	Mild idiopathic MR
Vorsanova et al. (17)	209	3.8%	Mild and severe MR-congenital malformations
Viot et al. (16)	17	23%	Major criteria: MR, dysmorphic features Minor criteria: family history, convulsive and behavioural disorders
Anderlid et al. (1)	44	13%	Severe MR (n=27), dysmorphic features (n=31), family history (n=14)
Joyce et al. (8)	93	2.2%	Idiopathic MR
Lamb et al. (12)	43	2.3%	MR and dysmorphic features
Turner and Partington (15)	20	0%	Idiopathic MR
Ballif et al. (3)	154	2.6%	ND

MR: mental retardation

With the available experience, the results of cryptic chromosomal rearrangement studies are variable but the frequency of positive diagnostic findings apparently depend very much on selection criteria of the patients, screening method, and number of screened subtelomeric regions.

As these molecular techniques (FISH) for testing subtelomeric rearrangements are time consuming and expensive, an alternative approach may be a new technique of multiplex amplifiable probe hybridisation (MAPH). Short probes, each recognising a unique region of genome DNA, can be recovered and amplified quantitatively following hybridisation to genomic DNA. The amount of each probe will be proportional to the copy number of the corresponding sequence in the test DNA (2). Comparative genomic hybridization (CGH) allows the genome-scale detection of complete and partial chromosome gains and losses, and might be a powerful tool in the search for small gendose changes in the total genome (5).

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Part 3

General Discussion

Diagnostic investigations in mental retardation and implications for medical care in ageing residents

Content Part 3

1 INTRODUCTION

Most Dutch mentally retarded adults are residents of institutions for the mentally handicapped. Presently, the large majority of these adults have no etiologic diagnosis. We expected that systematic etiologic screening of such an institution (Huize Assisië - Stichting Prisma) would increase the number of diagnoses. Further, we wondered about the changing phenotypes in ageing mentally retarded patients, not only the change in physical appearance, but also diagnosis-related medical comorbidity and behavioural problems that occur with age. Better knowledge of medical and behavioural problems in older mentally retarded patients can be used to improve prevention and care. Preventive management offers an important opportunity to minimise complications in children and adults with special health care needs, and the key to preventive management is a specific diagnosis and approach (Wilson and Cooley 2000).

2 DIAGNOSTIC INVESTIGATIONS IN MENTALLY RETARDED ADULTS

In the present study, the diagnostic approach was initially different for 2 groups of residents. In residents with Down syndrome (n=87), a clinical examination and routine cytogenetic studies on cultured peripheral lymphocytes were done to confirm trisomy 21. In the second group, residents were clinically and technically extensively investigated. Before systematic evaluation only 21.8% (103/471) of all patients had a known diagnosis. After this survey, 47.6% (224/471) of the investigated patients had a definite diagnosis explaining the MR (See table 1). Since this population consisted mainly of older mentally retarded males, data on early childhood, developmental milestones, childhood behaviour and medical history were not always complete.

For specific syndromes clinical features and behavioural phenotype are usually well known only in childhood. Better insight into the change with age of clinical features and behavioural phenotype may be of help for future clinical diagnosis in adults with MR. The effect of advancing age on dysmorphic features and the use of medication such as anti-epileptics, which lead to coarsening of the face, often render the diagnostic process difficult. The presence of severe spasticity, contractures and deformities also often preclude instant recognition of a genetic syndrome. A specific behavioural phenotype may be of help in making a diagnosis. Conversely, the recognition of a specific syndrome may help to predict (and sometimes prevent) aberrant behaviour. With advancing age behavioural problems may change e.g. decrease because of inactivity (as in Angelman syndrome), or increase when undiagnosed sensory problems are present as occurs frequently in Down syndrome. Speech problems may lead to behavioural problems as we observed in Cri du chat syndrome adults.

Technical investigations in the present study included standard cytogenetic investigation (GTG banding) on cultured peripheral lymphocytes. In a selected group of patients fluorescence in situ hybridisation studies (FISH) were performed, based on the presence of specific clinical features. Recently, Knight et al (1999) reported a frequency of 7.4% of subtle telomeric chromosome rearrangements in children with moderate to severe mental retardation. In the present study subtelomeric microdeletion studies were reserved for a selected group of 13 patients, with normal results.

Fragile X syndrome (expansion of the CGG repeat in the FMR-1 gene) was investigated in the presence of a positive family history (maternal MR) and/or the presence of clinical features of the syndrome.

Metabolic investigation was systematically done in 306 of the 471 investigated

mentally retarded patients. Practical problems were often present, since collection of 24-hours urine is difficult to organise in institutionalised MR adults because of incontinence or inability to co-operate with the technique of urine collection. In a small group of patients (n=15) it was not possible to obtain a urine sample for metabolic screening. Patients with Down syndrome (n=87) or with a diagnosis made in the past (n=63) were not investigated for metabolic disturbances. There were 7 patients with a previous diagnosis of a metabolic disorder, namely phenylketonuria (n= 5), mucopolysaccharidosis type III (Sanfilippo syndrome, type A) (n=1) and mucopolysaccharidosis type VII (Sly syndrome) (n=1). Of the total group of 306 patients screened for inborn errors of metabolism, only 5 (5/306; 1.6 %) were diagnosed with a "true" metabolic disease. In 4 patients this diagnosis explained the MR, namely GM1-gangliosidosis type 3 (n=1) and S-sulfocysteinuria (n=3). These patients all presented specific clinical symptoms that suggested the presence of a metabolic disease, as well as neurodegenerative behavioural problems. In 5 cases, a metabolic disorder was diagnosed that did not explain the MR. One patient was diagnosed with Niemann-Pick syndrome type B. Three had hyperprolinemia type 1, and one had cystinuria. Screening for Jaeken syndrome (Congenital Disorders of Glycosylation; CDG syndrome) was done for the first time on a large scale (n=144), but no patient was diagnosed. The number of patients with this syndrome among institutionalised mentally retarded may not be as high as previously thought. In a small number of patients (n=6) a clinically suspected diagnosis of Smith-Lemli-Opitz syndrome was not confirmed. The yield of screening for metabolic diseases apart from those which had already been previously diagnosed, was thus low in this cohort of institutionalised mentally retarded adults. In 24 patients we observed repeatedly abnormal values of certain metabolites without known significance.

Based on the experience in the present institution, screening of metabolic disorders in older institutionalised mentally retarded adults can be restricted to those patients with neurodegenerative features or behavioural problems (Van Buggenhout et al 2001).

In the present institution, only a small number of patients was selected for magnetic resonance imaging (MRI) (n=14) or computed tomography (CT) (n=11) of the brain (criteria: MR and neurological problems), due to budget restrictions. Even in this highly selected group few abnormalities were found and none of these were diagnostic. The American College of Medical Genetics recommends neuro-imaging in patients without a known diagnosis especially in the presence of neurological symptoms, macrocephaly, microcephaly or cranial contour abnormalities. In most situations MRI is the testing modality of choice (Curry et al

1997). Brain imaging is especially difficult in severely and profoundly mentally retarded patients, since this investigation has to be performed in hospitals and light anaesthesia is required to obtain good qualitative results. Often, there is no evolutionary comparison possible, since brain CT or MRI was never performed before. Follow-up brain imaging studies can be of help for making diagnosis at an older age, for further delineation of the natural history of syndromes and for early prevention of syndrome related complications (Curry et al 1997).

A large number of patients (n=69) was diagnosed with an acquired disorder, and in almost one third of these patients infectious agents in the postnatal period (i.e. meningitis, encephalitis and systemic sepsis) were the cause of the MR. The diagnosis of these acquired disorders was important for genetic counselling purposes. For several patients with a previous diagnosis of birth complication or perinatal asphyxia, this diagnosis was not convincing (not well documented) and such patients were included in the study. In some cases a genetic diagnosis was subsequently made (i.e. Angelman syndrome and Cri du chat syndrome).

Genetic counselling of the families was provided. Long-term follow-up of the patients and re-evaluation to obtain an accurate diagnosis should be included in the diagnostic process.

Table 1: The presence of a (re-evaluated) diagnosis before and after the systematic survey of the 471 investigated patients present institution. In 224 patients the diagnosis explained the mental retardation. In 14 more patients, the diagnosis did not explain the mental retardation: five had a numerical chromosomal disorder, four an autosomal dominant disorder and five a metabolic disorder

	Number of patients with a diagnosis **before** the systematic investigation (n=103)	Number of patients with a diagnosis **after** the systematic investigation of 471 patients (n=224)
Chromosomal disorders		
Autosomal disorders		
Numerical	40 (Down syndrome)	87 (Down syndrome)
Structural	2	7
Sex-chromosomes		
Numerical	-	1 (and in 5 not explaining the MR)
Monogenic disorders		
Autosomal dominant	7	10 (and in 4 no clear relation with MR)
Autosomal recessive		
Syndromic	2	9
Metabolic disorders	7	11 (and in 5 not explaining the MR)
X-linked disorders		
Fragile-X	14	16
Syndromic	-	2
Nonspecific	-	4
Central nervous system malformations	8	8
Acquired disorders		
Prenatal	3	15
Perinatal	6	27
Postnatal	14	27
Total	103	224

Note: Only patients in whom a genetic defect was documented at the molecular level were diagnosed as having definite X-linked non-syndromic mental retardation (XLMR). The number of patients with non-specific XLMR may well be much higher since 35 males (from 32 families) with idiopathic MR had a family history and pedigree data compatible with XLMR.

3 IMPLICATIONS OF SYSTEMATIC SCREENING OF MENTALLY RETARDED INSTITUTIONALISED ADULTS

3.1 EDUCATIONAL AND SOCIO-ECONOMIC IMPLICATIONS

Children with mild mental retardation attend schools for children with learning difficulties. As adults, they will be employed in sheltered working places and live independently or in sheltered homes. Moderately mentally retarded children will attend special schools, and as adults they are in sheltered working places and become institutionalised at some point in their lives, depending on their home situations. Patients with severe and profound MR will need as much as possible individual speech training and motor skill training, but they will be dependent on either home care or institutionalised care.
Traditionally, attention was focused on MR children, adolescents and young adults, while the characteristics and needs of middle and old aged MR adults are still poorly documented and understood (Seltzer and Kraus 1987; Flórez 1989; Evenhuis and Nagtzaam 1999).

3.2 MEDICAL AND BEHAVIOURAL PROBLEMS

3.2.1 Medical problems common to all mentally retarded adults

Comorbidity denotes a situation where a person has more than one disease or medical condition at the same time. Congenital disorders are rarely found as a single condition and most often involve multiple organ systems. The normal ageing process adds to these congenital disorders. Moreover, the pathogenic factors that lead to the MR, may add new features to the ageing individual in the brain or in other organs.

In the general population, the most frequent problems associated with age are cardiovascular problems, hypertension, cancer, diabetes, urinary tract infections and dementia. In mentally retarded residents specific problems besides these general problems appear with ageing, and these are related with the etiological diagnosis.

In most individuals with mental retardation their cognitive level does not seem to decline with advancing age, except for Down syndrome, where a decline in cognitive capacities is frequent (Silverstein et al 1988).

Problems that are more frequently reported among the elderly mentally retarded are visual and hearing loss, mobility problems with progressive motor impairment, epilepsy, language difficulties, emotional and/or psychiatric problems (Seltzer and Krauss 1987).

Cardiovascular, digestive, musculoskeletal, hearing and vision loss, respiratory and neoplastic problems are found in all levels of MR, with a roughly similar frequency. An exception may be that a significant higher incidence of musculoskeletal problems was apparent in one study of severely and profoundly retarded patients, aged 45-64 years (Janicki and Jacobson 1986). The risk of fractures and other musculoskeletal trauma has received special attention because fractures are a common medical problem in the mentally retarded, and certainly in the group of females (Tannenbaum et al 1989). They often result in considerable discomfort, loss of independent function and complications related to inactivity. In the age groups of 45 to 64 years, this risk was increased. A high morbidity and mortality of 12 to 20% is associated with hip fractures. The presence of seizures did not seem to result in an increased risk of fractures. However, the use of drug therapy carbamazepine, valproic acid and phenobarbital was associated with higher fracture risk (Tannenbaum et al 1989). Gastrointestinal problems are often present in bedridden patients, notably reflux, stomach ulceration and constipation.

Ophthalmological and hearing problems are frequently present. The diagnosis of these problems is difficult in severely and profoundly mentally retarded. In patients with mild or moderate mental retardation standardised screening methods for hearing such as play audiometry, speech audiometry or whisper test can be used and vision can be tested by using the Landolt ring chart. In the groups of patients with more severe level of mental retardation, hearing impairment can be tested by free field audiometry and distant vision with Burghardt picture charts (Van Buggenhout et al 1999).

Persons with more serious levels of MR are at a higher risk for health problems. It has been estimated that severely mentally retarded persons have 2.7 times, and mildly mentally retarded persons 2.2 times the number of health problems that persons without MR have (van Schrojenstein Lantman-de Valk et al 1997). In mildly mentally retarded persons a higher prevalence of deafness, obesity, fractures, skin problems and hemorrhoids was found. Severely mentally retarded persons have so many other problems that some of the minor health problems found in the mildly mentally retarded persons, are not recognised (van Schrojenstein Lantman-de Valk 1998).

In this study, we evaluated neurological abnormalities in patients with idiopathic MR (n=233; 215 males and 18 females). Neurological findings were present in 47 patients with in 45 central paresis and/or dyskinesia and/or ataxia. Seizures were present in one third of the patients (n=77) and this correlated with a more severe level of MR. Patients with severe MR had more neurological problems.

3.2.2 Behavioural problems common to all mentally retarded adults

In the group of profoundly and severely mentally retarded persons, the presence of congenital disorders, major central nervous system disorders, sensory handicaps such as blindness, strabismus and deafness, severe motor disabilities such as cerebral palsy, and seizures, will obviously limit social contacts. When such persons cannot express themselves, this lack of active communication may provoke aggressive behaviour and self mutilation (Menolascino et al 1986).

Although moderately mentally retarded patients possess some degree of receptive and expressive language, self-care and daily living skills, they are at high risk of behavioural problems. In times of stress, they often react with maladaptive behaviour, such as excessive sadness, withdrawal or avoidance. Without adequate support they are likely to develop depression (Menolascino et al 1986).

Severe behavioural problems or psychiatric illness are twice as frequent as in those without mental retardation. The frequency of dementia in the group of patients without Down syndrome is probably comparable with the frequency in the general population (Visser 1999). Depression and severe hearing loss are difficult to differentiate from dementia, especially in persons with poor verbal capacities. Tuinier and Verhoeven (1992) concluded that diagnosing depression in persons with poor verbal capacities is very difficult and often impossible.

More knowledge regarding comorbidity would help to improve treatment for mentally retarded persons who often have problems in verbalising symptoms and signs (Day and Jancar 1994). It would be interesting to learn in prospective randomised studies whether educational programs for mentally retarded adults really improve behaviour. Overmedication because of behavioural problems should be avoided in older patients since the sensitivity to the drug and the pharmacokinetic profile may be altered.

3.2.3 Diagnosis-related specific medical and behavioural problems

Persons with Down syndrome are at higher risk for a number of specific conditions. However, comorbidity is not well described for other genetic syndromes (Evenhuis and Nagtzaam 1999). The present study intended to collect more information on comorbidity in Down syndrome and other genetic syndromes.

3.2.3.1 Down syndrome

Disorders due to a chromosomal imbalance often result in a more rapid deterioration and frequently there is a shorter life span. This is clearly the case for Down syndrome (DS) where specific brain changes are induced by imbalance of the genetic material of chromosome 21. Comorbidity is well described in DS and includes congenital malformations (notably cardiac and gastro-intestinal malformations), immunologic problems, leukemia, hepatitis, hypo- and hyperthyroidism, sensory impairments with visual and hearing impairment, Alzheimer dementia, psychiatric disorders, atlanto-axial dislocation, obesity, cardiovascular disorders, epilepsy, and dental problems. A decline with age in some of the cognitive capacities is observed frequently (Silverstein et al 1988). Guidelines for optimal medical care were described by a group of international experts (Pueschel et al 1995). Borstlap et al 2000 described recently guidelines for children with DS. Mitral valve prolapse and aortic regurgitation have been found to be more prevalent in adults with Down syndrome, and the clinical diagnosis may be confirmed by echocardiographic examination (Pueschel et al 1995). Behavioural and psychiatric disorders are frequently present in the group of patients with DS and to such patients, specific psychotherapy and medication should be offered (Pueschel et al 1995; Van Allen et al 1999).

In our group of DS patients (n=96) dementia was present in almost 20% of the patients, increasing to more than 40% of those above the age of 50 years. Epileptic seizures were present in 50% of the patients with dementia. Vision loss was present in 83% of the patients and in one-third this vision loss was at least moderate. With age this percentage increased significantly. Moderate or severe hearing loss was present in 70%. Thyroid function was abnormal in almost 50% of the investigated patients. These findings confirm the necessity of the implementation of a yearly screening in residential DS adults. Such a formal screening program does not yet exist in most institutions. The yearly physical examination by the general practitioner of the institution should include heart auscultation, screening for thyroid dysfunction, for early loss of visual acuity and hearing, and should exclude medical or psychiatric causes leading to a dementia-like picture. These recommendations are

comparable with the Guidelines for optimal medical care (Pueschel et al 1995). Objective evaluation of cognitive functioning to diagnose early onset dementia can be done by using one of the following questionnaires such as "Sociale Redzaamheidsschaal" (SRZ) (Daily living skills) (Kraijer and Kema 1990), "DMR" (the Dementia Questionnaire for Mentally Retarded Persons) (DVZ; Dementie Vragenlijst voor Verstandelijk Gehandicapten) (Evenhuis et al 1991) and the "Observatielijst Ouderwordende Bewoners (OOB) (Observation List for Ageing Residents) (Hoefnagel 1989).

3.2.3.2 Cri du chat syndrome.

In the Cri du chat syndrome (deletion of the terminal short arm of chromosome 5) the dysmorphic features become less striking with advancing age. However, marked growth retardation continues into adulthood and results in short stature, poor weight gain and microcephaly. The face lengthens and teeth are abnormally erupted (Niebuhr 1978). Scoliosis is often present in older patients and is severe in half of the cases (O'Brien and Yule 1995).

The findings in our group of patients (n=7) included a history of feeding difficulties with poor sucking, chewing and swallowing in almost all patients, and these problems were still present at an older age. Four patients developed scoliosis. In childhood the problems of self mutilation, head banging, scratching, biting, and cruelty to others were often severe. With advancing age these problems decreased. They did like teasing, and were often hyperactive. Although their personality was generally pleasant, periods of destructive behaviour and aggression were present. Most of these periods of behavioural problems were related to the inability of verbal and/or non-verbal communication.

Stimulation and revalidation of sucking, chewing and swallowing functions by occupational therapists and speech therapists may lead to improvement of feeding. Offering skills for the use of non-verbal communication from an early age, may be of help to prevent behavioural problems.

3.2.3.3 Angelman syndrome

In Angelman syndrome the clinical and behavioural features change with age and the phenotype can be rather non-specific. In adult patients there is coarsening of the face. Thoracic scoliosis is frequently present, mostly in females. Mobility decreases with advancing age, with difficulties of walking and some patients becoming wheelchair bound (Buntinx et al 1995). Stimulation and physiotherapy may be of help to prevent other complications related to the inactivity. Epileptic seizures are still present in adulthood (Laan et al 1997).

The findings in our patients (n=3) showed severe neurological complications of tremor, spasticity and coordination problems, resulting in severe loss of function. Craniofacial features were atypical. They had short stature, epileptic seizures, microcephaly, brachytelephalangy and absent speech. Two patients presented at an older age a change in day-night rhythm. More stimulation of the patients during the day was helpful and led to improved sleep at night. This phenomenon of a disturbed circadian rhythm warrants further investigation. At a young age Angelman syndrome patients are physically hyperactive (actors). With ageing, patients become passive, but seek variation by watching other persons (people-watchers). We hypothesize that absence of variation makes them uncomfortable and leads to behavioural problems. At all ages patients are more interested in persons than in objects. Increasing social activities during the day might thus improve both behavioural problems and sleeping at night (Van Buggenhout et al, 2000).

3.2.3.4 Fragile X syndrome

In the fragile X syndrome seizures are observed in approximately 20% of young affected males, with a lower prevalence in adult males and females (5%). Recurrent otitis media and sinusitis are present in 50% of cases and need adequate intervention to prevent complications. In 30 to 50% of cases ophthalmologic help is needed because of strabismus, myopia and hyperopia. Attention deficit disorder and hyperactivity are present in childhood. In adulthood some individuals may show aggressive behaviour (De Vries et al 1998).

Major medical complications in the present group of patients (n=16) with the fragile X syndrome included epileptic seizures (n=5), moderate hearing loss (n=3) and severe loss of visual acuity (n=3). One patient with severe loss of visual acuity, had divergent strabismus and myopia. The second patient had divergent strabismus and papillary atrophy. The third patient had bilateral cataracts. Behavioural problems (n=8) included hyperactivity, self-mutilation with hand biting, and aggression. In the ageing fragile X patient, special attention should be given to detect early visual and hearing problems and therefore regular screening should be provided. Speech therapists and physiotherapists can ameliorate language and motor problems.

3.2.3.5 X-linked mental retardation-marfanoid habitus syndrome

In X-linked mental retardation-marfanoid habitus syndrome (Lujan-Fryns syndrome) major clinical criteria include mild to moderate mental retardation, emotional instability, shyness, psychotic behaviour, marfanoid habitus with long hyperextensible fingers and toes, short halluces and long second toes (Fryns and

Buttiens 1987).

In the 2 moderately mentally retarded adults of the present institution with ectomorphic habitus, triangular face, narrow palate and hypernasal voice, no psychiatric problems were observed. The first patient presented some autistic-like behaviour and both males were very shy.

3.2.3.6 IL1RAPL gene mutation family

In the family with the mutation in the IL1RAPL gene non-specific mental retardation was present and the natural history and medical complications are unknown. Speech was peculiar and their voice was hypernasal. Behavioural problems included self mutilation and aggression.

3.2.3.7 Metabolic disorders

Those metabolic disorders that cannot be controlled therapeutically will cause a decline in the function of several organs, including the brain, thereby resulting in a more rapid deterioration. The exact pathogenesis of metabolic disorders is not always known and the variability in appearance and rate of expression of the individual lipid and protein components suggests that there are wide differences in vulnerable periods in specific pathways of myelinisation of the white matter (Kinney et al (1994)).

The four adults in this study, diagnosed with a metabolic disease, explaining the MR, all presented specific clinical symptoms and neurodegenerative or behavioural problems. In 5 other patients, a newly diagnosed metabolic disorder could not explain the etiology of MR.

3.2.3.8 Fountain syndrome

Fountain syndrome was first reported in 1974 in a family with 4 affected sibs who had mental retardation, deafness and skeletal abnormalities (Fountain 1974). In our study the clinical picture becomes more clear with advancing age, with extreme coarsening of the face, severe hearing impairment and slow decline in mental functioning.

3.3 EARLY DIAGNOSIS AND TREATMENT OF COMORBIDITY ACQUIRED LATER IN LIFE

3.3.1 Aim

The United States Healthy People 2000 program (U.S. Public Health Service, 1991) set forth 3 goals: 1. Increase the span of healthy life, 2. Reduce health disparities among individuals and, 3. Improve access to preventive services (Wilson and Cooley 2000). The main goal is the improvement in quality of life.

Preventive management of genetic disorders can be defined as the avoidance or amelioration of complications in the patient with a genetic disease. These complications, depending on the level of MR, include chronic diseases and physical problems (e.g. sensory problems, gastro-intestinal problems, neurological disorders), psychiatric problems (e.g. dementia) and behavioural and communication problems (e.g. inappropriate behaviour, changing behaviour). Medication should be limited and overmedication elimited.

3.3.2 Medical care plan

There is a need to design a preventive care plan, including daily activities and therapies, for adults. However, each individual patient has specific problems which are compounded by differences in mental level and in motor capacities, and therefore it is not possible to create one "golden standard" care plan. A personal caregiver or parent, who best knows the mentally retarded individual, is of great value, since they may recognise problems in an early stage.

Follow-up and regular screening on a yearly basis by the general practitioner of the institution of vision, hearing, thyroid function, dental status, psychiatric problems and behavioural problems should be included in the preventive medical program for all mentally retarded adults. Changes in levels of general functioning can be measured year by year. In addition, prevention of specific complications known to occur with genetic syndromes is warranted. Since for many syndromes the natural history is poorly defined, long-term follow-up is needed.

Wilson and Cooley (2000) described preventive management of children with 30 rare congenital anomalies and syndromes. Medical checklists were developed for 2 anomalies (spina bifida and cerebral palsy), 2 associations and 26 syndromes, including 16 related with mental retardation. Of these extensively described MR conditions, Down syndrome, Prader-Willi syndrome, Shprintzen syndrome (Velo-cardio-facial syndrome), Fragile-X syndrome, tuberous sclerosis

(Bourneville), Brachmann- de Lange syndrome, mucopolysaccharidoses, cerebral palsy and spina bifida were all found in Huize Assisië-Stichting Prisma. Other syndromes that we found in this institution, such as the Cri du chat syndrome and Angelman syndrome, were discussed only briefly. However, with the present data and future research, it will be possible to construct similar checklists for these and other more rare syndromes.

4 RECOMMENDATIONS

1. Based on the results of this pilot study, nation-wide systematic etiologic-diagnostic screening is recommended. Every mentally retarded patient has the right to a diagnosis because of implications for himself, his family and the management of the institution.

2. Guidelines for systematic etiological surveys of institutions are proposed (see Addendum). Data collection on family history and perinatal and childhood medical data in adult mentally retarded patients is frequently very difficult. It is recommended that institutions keep all familial and medical data life-long and, preferably, indefinitely, to allow accurate genetic counselling in current or future family members at any time. Financial means have to become available to allow at least one MRI or CT of the brain for each mentally retarded patient without a known diagnosis in the presence of neurological symptoms, microcephaly, macrocephaly or cranial contour abnormalities.

3. This study stresses the importance of life-long follow-up of mentally retarded patients, especially of those with an etiologic diagnosis to learn more about the evolution of genetic syndromes and the occurrence of comorbidity in adulthood. Based upon these findings, diagnostic and therapeutic guidelines for the institution physicians will be continuously refined. Large-scale studies on comorbidity have only just started (Evenhuis and Nagtzaam 1999). After the etiological screening of large institutions more adult patients with rare syndromes will be diagnosed. This may in the end allow meaningful conclusions and recommendations concerning comorbidity and behavioural problems.

4. The present study shows that the recognition, follow-up and treatment of a diagnosis-related behavioural phenotype, is an integral part of the care for mentally retarded adults such as in Cri du chat syndrome and Angelman syndrome.

5 FUTURE STUDY AIMS

1. In the present study, we mainly focused on the systematic etiologic-diagnostic process, but we also came across medical and behavioural problems. Further evaluation of the persistent feeding problems at an older age in the Cri du chat syndrome, the change in day-night rhythm in Angelman syndrome and the severe loss of visual acuity in the fragile X syndrome in larger groups of patients is necessary. Specially designed studies about the validity of and yield of screening recommendations for comorbidity, behaviour in groups with known and unknown diagnoses, and the value of behavioural therapy are needed. Whether the outcome of better care indeed leads to better quality should also be studied. A nation-wide co-ordination centre can be helpful in registering ongoing studies. This centre may be helpful in offering easy access for general practitioners and for researchers, and may have a task in the education of general practitioners. This centre also may provide new research questions.

2. The implication of a diagnosis for the family should be evaluated. In the present study, we asked the parents or legal representatives for participation in this study. When a genetic diagnosis was obtained, genetic counselling was offered. Studying the psychological effects of these counselling sessions that were initiated from the institution can be informative, since normally, it is the parents or the general practitioner, who take the initiative for genetic counselling. In the present study, no permission was given in 84 of the 591 residents, even after a second letter, which contained more information on the investigation, was sent to the parents. Other methods, such as personally visiting the parents, may be more efficient. Since every person with MR has the right to obtain a diagnosis, an ethical question may rise whether the right of the mentally retarded person to have a diagnosis in order to prevent associated medical complications, can outweigh the right of family members to refuse diagnostic investigations.

3. Having a diagnosis has important consequences for the institution in planning medical, paramedical and educational staff. However, only prospective studies can measure the true impact of this statement. The cost for the institutions with a population of ageing residents is another aspect for future research.
   Decentralisation of institutional residential settings may lead to a different co-ordination of medical care. General practitioners are more frequently involved in the care program for the patients. Adequate training of general practitioners and paramedical staff members should be provided in this area of

specific problems. The creation and evaluation of multidisciplinary teams specialised in the field of MR may contribute towards a solution of this new problem.

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ADDENDUM

PROPOSED FLOW-CHART OF GENETIC INVESTIGATIONS IN INSTITUTIONALISED MENTALLY RETARDED ADULT PATIENTS

1 DIAGNOSTIC APPROACH

1.1 Diagnostic approach: first step: collaboration of general practitioner, specialised in MR and clinical geneticist

1. Written permission

2. Collection of clinical data:

History

A. Family history:

Three generation pedigree (stillbirths and miscarriages) - familial MR - sporadic patients - consanguinity - clinical photographs of relatives

B. Medical history:

Pregnancy - perinatal period - neonatal period (seizures - regression)

Clinical and behavioural follow-up since childhood - early biometric data - major events (surgery - specialist visiting) - hearing / vision - puberty - X-rays - laboratory - IQ tests - clinical photographs over time

Clinical examination

Biometric values (length, weight, head circumference, span, outer canthal distance (OCD), inner canthal distance (ICD), total hand length (THL), finger III length, ear length)

General aspect - craniofacial appearance (dysmorphic features) - thorax - abdomen - extremities - genitalia - neurology

Clinical photographs

Standard: face, profile, general view, hands and feet

Other structures on indication.

Behavioural examination

Interpretation of the standardised tests performed by the educational psychologist.

Technical investigations

A. Chromosomal investigation (GTG-banding)

B. DNA studies (based on clinical working diagnosis):

Fragile X syndrome (positive family history / clinical features)
Angelman syndrome (clinical features / neurology)
Prader-Willi syndrome (obesity / hyperphagia / history of neonatal hypotonia)
Rett syndrome (neurodegenerative problems / hand movements)

1.2 Discussion with an expert team

Clinical geneticist - neurologist - other specialists

1.3 Additional investigations on indication

- Special chromosomal investigations of blood (reverse-banding, high resolution banding, microdeletions (Fluorescence in situ hybridisation)) or investigations of other tissues
- Neuro-imaging: MRI or CT-scan (neurological problems - macrocephaly - microcephaly - cranial contour abnormalities - epilepsy)
- X-rays: e.g. hands - feet - skull (only if a specific syndrome or abnormality is suspected)
- Basic metabolic screening (neurodegenerative problems)
- Specialist visits

2 IMPLICATION OF DIAGNOSIS: GENETIC COUNSELLING AND FOLLOW-UP

2.1 Counselling of families - prenatal counselling

2.2 Follow-up of the patient

- Clinical re-evaluation: to study syndrome-related comorbidity or diagnostic re-evaluation.
- Behavioural re-evaluation
- New technical investigations such as:
  - microdeletion studies
  - non-specific XLMR studies
- Discussion with collegues (meetings).

Appendix

Contents

SUMMARY

Mental retardation (MR) affects 2 to 3% of the population. The definition of MR, proposed by the American Psychiatric Association include 3 criteria: 1. Significantly sub-average general intellectual functioning (IQ≤70), 2. Significant limitations in adaptive functioning in at least two of the following skill areas: communication, self-care, ability to live independently, social and interpersonal skills, use of public services, decision taking, functional academic skills, work, leisure, health and safety, 3.Onset before the age of 18 years.

More male than female individuals have MR. The male to female ratio shows an excess of males in severe MR of 20% and in mild MR of 40 to 80%, probably due to sex-linked genetic factors. The cause of MR remains unknown in almost 50% of the cases. In severe MR a single cause can be found in 50% and in mild MR in less than 20%, but this group has an increased percentage of familial MR. ***Chromosomal abnormalities*** (1.8 % to 41.6%), with more than 80% trisomy 21, are the best recognised common cause of severe MR. Mutations in a single gene - ***monogenic disorders*** - account for 20 to 25% of severe and 5 to 10% of mild MR. X-linked mental retardation is estimated to affect 20 to 25% of all mentally retarded males and 10% of mildly mentally retarded females, and are categorised non-specific (MRX) or syndromic (MRXS). The fragile X syndrome is the most frequent MRXS. Few mentally retarded patients with ***central nervous system malformations*** have been reported, probably due to few brain-imaging studies carried out on them. ***Acquired disorders*** account for 30 to 35% of severely and 15% of mildly mentally retarded patients, but this figure is probably an overestimation. A systematical etiologic-diagnostic survey was carried out in the Institution Huize Assisië - Stichting Prisma in the southern part of the Netherlands and resulted in the description and follow-up of several patients with dysmorphic features.

In **part 1** a general overview of the results in this population of 471 older mentally retarded institutionalised patients is presented (mean age 46 years; 92.6% males). ***Chromosomal abnormalities*** were found in 100 patients (21.2%). Of these, 87 had numerical autosomal abnormalities (all Down syndrome), 7 structural autosomal abnormalities and 6 numerical abnormalities of sex chromosomes. ***Monogenic disorders*** were diagnosed in 61 patients (13%) (14 autosomal dominant, 25 autosomal recessive and 22 X-linked conditions). In 1.7% (n=8) of the patients a ***central nervous system (CNS) malformation*** was considered the cause of the mental handicap. ***Acquired CNS disorders*** were diagnosed in 69 patients (14.6%) (prenatal cause (n=15), perinatal cause (n=27), postnatal cause (n=27)). In 233

patients (49.5% of the total sample; 215 males and 18 females) an ***idiopathic type of mental retardation*** was present. In this group several parameters were recorded: 1. positive family history of mental retardation (n=73), with special attention to patients with pedigree data compatible with X linked mental retardation (n=35, from 32 families); 2. dysmorphic features (n=41), which were associated with the severity of the MR; 3. neurological abnormalities (n=47); 4. epileptic seizures (n=78), which were positively correlated with the level of MR; 5. combination of microcephaly and micro-orchidism (n=3), which was higher than expected; 6. combination of macrocephaly and macro-orchidism (n=5), which was statistically significantly increased; 7. Consanguinity (n=9).

In **part 2**, attention was focused on the biomedical approach in older mentally retarded patients and on the natural history of different syndromes in this ageing group.

In the first part of **chapter 1** the population of patients with ***Down syndrome*** (DS) (n=96) is described. More than two third of the patients (i.e. 73%) were older than 40 years. A high percentage of mosaic trisomy 21 (12.6%) was found. Special attention was given to the patient who presented with ***Down-Turner phenotype*** (45,X/46,X,+21/47,XY,+21) and who was the oldest one in this population with DS. Most patients (82%) were moderately or severely mentally retarded. Dementia occurred up to 42.4% above the age of 50 years. One third of the patients had at least moderately reduced vision and this increased with age. A moderate, severe or very severe hearing loss was present in 70% of the patients. Thyroid dysfunction with increased (48%) or decreased (1%) TSH level was found in 49% of the patients examined for thyroid functions. A regular screening of all adult ageing patients with DS with special attention to the group of patients who are severely to profoundly mentally retarded is recommended in order to diagnose at an early stage dementia, depression, hypothyroidism or early loss of visual acuity and hearing.

In the second part of **chapter 1**, patients with other chromosomal abnormalities are described. In the ***Cri du chat syndrome*** the clinical phenotype becomes less striking with ageing. Some of the clinical characteristics become more evident such as long face, macrostomia and scoliosis. Most patients had periods of destructive behaviour, self mutilation and aggression. The patient with a deletion of the distal part of the long arm of chromosome 13 (***13q deletion syndrome***) was severely mentally retarded, had no major organ malformations, and had normal limb development with normal thumbs. The phenotype of ***Angelman syndrome*** (AS) is well known in childhood and adolescence, but in adulthood the phenotype can be rather aspecific. We noted severe neurological complications such as severe tremor,

spasticity and inco-ordination with severe loss of function in adults with AS.

In **chapter 2**, the clinical phenotype and follow-up data of the group of males with X-linked mental retardation (n=57) is described. The fragile X syndrome (FRAXA) was diagnosed in 16 and X-linked mental retardation with marfanoid habitus (Lujan-Fryns syndrome) in 2 patients. Non-specific XLMR (MRX) was diagnosed in 3 male sibs of a family, carrying a mutation in the IL-1 receptor accessory protein-like gene, and one male patient member of the MRX-44 family. In 35 other patients, from 32 families, with idiopathic MR, the family history, and pedigree data were compatible with non-specific XLMR.

In **chapter 3** the group of patients with metabolic disorders is described: 1. metabolic disorders as the cause of MR (i.e. phenylketonuria (PKU) (n=5), S-sulfocysteinuria (n=3), mucopolysaccharidosis type III (Sanfilippo A) (n=1) and GM1-gangliosidosis type 3 (n=1)), 2. metabolic disorders not explaining the MR (i.e. mucopolysaccharidosis type VII (Sly) (n=1), Niemann-Pick type B (n=1), cystinuria (n=1) and hyperprolinemia type 1 (n=3)), and 3. metabolic abnormalities of unknown significance. This study confirms that patients with idiopathic MR in combination with aberrant behaviour, neurodegenerative problems or dysmorphic features are candidates for performing metabolic screening tests.

In **chapter 4** patients with recognisable dysmorphic syndromes are reported (i.e. Zimmermann-Laband, Fountain and Björnstad syndromes). Further delineation of the clinical features and, where possible, follow-up data of these syndromes are presented. Special attention was given to the group of patients with dysmorphic features, but without a clinical diagnosis, and microdeletion studies with a selected panel of subtelomeric probes were performed.

In the first part of **part 3** the diagnostic approach in institutionalised older mentally retarded patients is discussed. Clinical features and behavioural phenotype are usually well known in childhood and adolescence, but may change with advancing age. A standard cytogenetic examination on cultured peripheral lymphocytes was performed in all patients. In a selected group of patients fluorescence in situ hybridisation (FISH) were performed based on the presence of specific clinical features. DNA studies for the fragile X syndrome (expansion of the CGG repeat in the FMR-1 gene) was done in the group of patients with clinical features of the syndrome and/or with a positive history of familial MR (maternal MR). Metabolic studies were systematically performed in 306 of the 471 investigated mentally retarded patients. The yield of screening for other metabolic disorders besides PKU and the clinically recognisable lysosmal storage disorders, which were previously diagnosed, was thus low in this institution. Based on the

experience in the present institution, screening of metabolic disorders in older institutionalised mentally retarded adults can be restricted to those patients with neurodegenerative features or behavioural problems. Brain imaging studies were done in a small number of patients, and even in this highly selected group few abnormalities were found and none of these were diagnostic.

In the second part of part 3 medical and behavioural problems of ageing in the general population of mentally retarded adults, and diagnosis-related problems are discussed. Persons with more serious levels of MR are at a higher risk for health problems. Cerebral palsy, visual and hearing loss, mobility problems, epilepsy, language difficulties, emotional and/or mental problems are frequently reported among the elderly mentally retarded persons and add a new dimension to ageing. These problems result in limiting social contacts and often result in behavioural problems such as aggressive behaviour and self mutilation in the severely to profoundly mentally retarded. Moderately mentally retarded persons may react with maladaptive behaviour and are candidates to develop depression. Comorbidity is, besides in Down syndrome, not well described in other genetic syndromes. In this institution we studied medical and behavioural problems in Down syndrome as well as in other diagnostic subgroups of patients. Recommendations are formulated for the care for mentally retarded adults.

In addendum a flow-chart of genetic investigations in mentally retarded adult patients is proposed.

SAMENVATTING

Mentale retardatie komt voor bij 2-3% van de bevolking. Volgens de "American Psychiatric Association" spreekt men van mentale retardatie wanneer voldaan wordt aan 3 criteria: 1. Wezenlijke beperkingen in het huidig functioneren met een IQ ≤ 70; 2. Belangrijke beperkingen in minstens 2 van de volgende gebieden van adaptief gedrag: communicatie, zelfzorg, huishoudelijke vaardigheden, sociale vaardigheden, maatschappelijke vaardigheden, zelfbepaling, functionele schoolse vaardigheden, werk, vrije tijd, gezondheid en veiligheid; 3. Een aanvang voor het 18e levensjaar.

Er zijn meer mannen met mentale retardatie dan vrouwen. De man-vrouw verhouding toont een mannenoverschot van 20% in de groep ernstig verstandelijk gehandicapten, en 40-80% in de groep licht verstandelijk gehandicapten, waarschijnlijk als gevolg van geslachtsgebonden genetische factoren. In de helft van de gevallen van mentale retardatie is de oorzaak onbekend. In de groep ernstig verstandelijk gehandicapten wordt in de helft van de gevallen één enkele oorzaak gevonden. In de groep licht verstandelijk gehandicapten wordt één enkele oorzaak in minder dan 20% van de gevallen gevonden, maar komt er een hoger percentage familiale verstandelijke handicap voor.

Chromosomale afwijkingen (1.8-41.6%) vormen de belangrijkste oorzaak in de groep ernstig verstandelijk gehandicapten en hiervan heeft méér dan 80% trisomie 21 (Down syndroom). Bij 20-25% van de ernstig verstandelijk gehandicapten, en 5-10% van de licht verstandelijk gehandicapten zijn mutaties in één enkel gen - ***monogene afwijkingen*** - verantwoordelijk. X-gebonden mentale retardatie is verantwoordelijk voor 20-25% van alle mentale retardatie bij mannen en voor 10% van de licht mentale retardatie bij vrouwen. X-gebonden mentale retardatie wordt in 2 groepen onderverdeeld: de niet-specifieke (MRX) en de syndromale (MRXS). De meest voorkomende syndromale vorm is het fragiele X syndroom. Slechts een gering aantal verstandelijk gehandicapten met ***centraal zenuwstelsel afwijkingen*** werd gerapporteerd, waarschijnlijk omdat weinig beeldvormend onderzoek van de hersenen wordt uitgevoerd bij verstandelijk gehandicapten. Verworven aandoeningen worden verantwoordelijk geacht bij 30-35% van de ernstig mentaal en bij 15% van de licht mentaal gehandicapten, doch hier vormen de cijfers waarschijnlijk een overschatting.

Een systematisch etiologisch-diagnostisch onderzoek werd uitgevoerd in het instituut voor verstandelijk gehandicapten Huize Assisië - Stichting Prisma in Zuid-Nederland. Dit resulteerde in de beschrijving en follow-up van verschillende verstandelijk gehandicapten.

Deel 1 beschrijft het algemeen overzicht van de resultaten van deze geïnstitutionaliseerde populatie van 471 oudere verstandelijk gehandicapten gegeven (gemiddelde leeftijd: 46 jaar; 92.6% mannen). Bij 100 patiënten (21.2%) werd een ***chromosomale afwijking*** gevonden met een numerieke afwijking bij 87 (allen Down syndroom), een structurele afwijking bij 7, en bij 6 patiënten een numerieke afwijking van de geslachtschromosomen. ***Monogene afwijkingen*** werden gediagnosticeerd bij 61 patiënten (13%) (autosomaal dominant (n=14), autosomaal recessief (n=25) en X-gebonden (n=22)). Bij 8 patiënten (1.7%) was een ***afwijking van het centraal zenuwstelsel*** de oorzaak van de verstandelijke handicap. Een ***verworven aandoening*** vormde de verklaring bij 69 patiënten (14.6%) (prenatale oorzaak (n=15), perinatale oorzaak (n=27), en postnatale oorzaak (n=27)). In de resterende groep van 233 patiënten (49,5%; 215 mannen en 18 vrouwen) werd geen echte diagnose gevonden (idiopathische mentale retardatie). In deze groep werd een associatie met bepaalde factoren verder nagekeken: 1. Familiaal voorkomen van mentale handicap (n=73), waarvan 35 met X-gebonden mentale retardatie; 2. De aanwezigheid van dysmorfe kenmerken (n=41); deze waren bovendien gecorreleerd met de ernst van de mentale handicap; 3. Het voorkomen van neurologische afwijkingen (n=47); 4. Aanwezigheid van epilepsie (n=78), hetgeen bovendien gecorreleerd was met de ernst van de verstandelijke handicap; 5. Het voorkomen van microcefalie samen met micro-orchidie (n=3), hetgeen frequenter was dan verwacht; 6. De aanwezigheid van de combinatie macrocefalie en macro-orchidie (n=5), hetgeen eveneens significant meer voorkwam; 7. Consanguiniteit (n=9).

In **deel 2** wordt de aandacht gevestigd op de biomedische aanpak bij oudere verstandelijke handicapte personen en op het natuurlijk proces van veroudering bij verschillende syndromen.

In het eerste gedeelte van **hoofdstuk 1** wordt de populatie patiënten met Down syndroom (DS) beschreven (n=96). Meer dan twee derde van deze patiënten (73%) was ouder dan 40 jaar. Een hoog percentage patiënten (12.6%) had trisomie 21 mosaicisme. Speciale aandacht werd geschonken aan een patiënt met het Down-Turner syndroom (45,X/46,X,+21/47,XY,+21), die tevens de oudste was van de totale groep DS patiënten. De meeste patiënten (82%) waren matig tot ernstig verstandelijk gehandicapt. Boven de leeftijd van 50 jaar kwam dementie voor tot 42.4%. Eén derde van de patiënten had minstens matig verminderde visus en dit percentage nam toe met de leeftijd. In 70% van de patiënten was matig, ernstig of zeer ernstig gehoorsverlies aanwezig. Bij de patiënten die een schildklier-onderzoek ondergingen werd een gestoorde schildklierfunctie gevonden bij 49% met verhoogd

(48%) of verlaagd (1%) TSH. Regelmatig onderzoek van alle ouderwordende volwassen DS patiënten, met speciale aandacht voor de groep patiënten met ernstige en diepe verstandelijke handicap, is aanbevolen om vroegtijdig dementie, depressie, hypothyroidie of vroegtijdig verlies van visus en gehoor op te sporen.

In het tweede gedeelte van dit hoofdstuk worden patiënten met andere chromosomale afwijkingen beschreven. Bij het Cri du chat syndroom wordt het fenotype over het algemeen minder duidelijk met toename van de leeftijd. Sommige klinische kenmerken echter worden duidelijker zoals het langwerpige gezicht, macrostomie en de scoliosis. De meeste patiënten hadden periodisch destructief gedrag, automutilatie en agressie. De patiënt met een distale deletie van de lange arm van chromosoom 13 (13q deletie syndroom) was ernstig verstandelijk gehandicapt maar hij had geen majeure orgaanafwijkingen. De ledematen en duimen waren normaal ontwikkeld. Het fenotype bij het Angelman syndroom (AS) is goed gekend bij kinderen en adolescenten, echter bij volwassenen kan het fenotype atypisch zijn. Bij onze volwassen AS patiënten werden ernstige neurologische complicaties met ernstige tremor, spasticiteit en coördinatieproblemen leidend tot een ernstig functieverlies waargenomen.

In **hoofdstuk 2** wordt het klinisch beeld en de follow-up gegevens van de groep mannen met X-gebonden mentale retardatie (XLMR) (n=57) beschreven. Het fragiele X syndroom (FRAXA) werd gediagnosticeerd bij 16 patiënten en X-gebonden mentale retardatie met marfanoide habitus (Lujan-Fryns syndroom) bij 2 patiënten. Niet-specifieke XLMR (MRX) werd gediagnosticeerd bij 3 broers uit één familie, waar een mutatie in het "IL-1 receptor accessory protein-like gene" werd gevonden, en bij één mannelijk lid van de MRX-44 familie. Bij 35 andere patiënten, afkomstig uit 32 families, met idiopathische MR stemden familiale anamnese en stamboomgegevens overeen met niet-specifieke XLMR.

Hoofdstuk 3 beschrijft de groep patiënten met een metabole ziekte met de volgende classificatie:
1. Metabole ziekten die de verstandelijke handicap verklaren: Fenylketonurie (PKU) (n=5), S-sulfocysteinurie (n=3), muco-polysaccharidose type III (Sanfilippo A) (n=1), en GM1-gangliosidose type 3 (n=1); 2. Metabole ziekten die de verstandelijke handicap niet verklaren: mucopolysaccharidose type VII (Sly) (n=1), Niemann-Pick type B (n=1), cystinurie (n=1), en hyperprolinemie type 1 (n=3); 3. Metabole afwijkingen met onbekende betekenis. Deze studie bevestigt dat patiënten met idiopathische verstandelijke handicap gecombineerd met afwijkend gedrag, neurodegeneratieve problemen of dysmorfe kenmerken kandidaat zijn voor verder metabool nazicht.

In **hoofdstuk 4** worden patiënten met herkenbare syndromen beschreven:

Zimmermann-Laband syndroom, Fountain syndroom en Björnstad syndroom. De klinische kenmerken worden verder beschreven en de follow-up gegevens worden waar mogelijk meegedeeld. Speciale aandacht werd gegeven aan de groep patiënten met dysmorfe kenmerken zonder diagnose, waar microdeletie studies met een geselecteerd panel probes werd uitgevoerd.

In het eerste gedeelte van **deel 3** wordt de diagnostische aanpak bij geïnstitutionaliseerde oudere patiënten besproken. De klinische kenmerken en de gedragskenmerken zijn meestal goed gekend bij kinderen en adolescenten, maar deze kunnen wijzigen met toenemende leeftijd. Een standaard cytogenetisch onderzoek op gekweekte perifere lymfocyten werd uitgevoerd bij alle patiënten. Bij een groep patiënten, geselecteerd op basis van specifieke klinische kenmerken, werden fluorescentie in situ hybridisatie (FISH) technieken uitgevoerd. DNA onderzoek naar het fragiele X syndroom (expansie van de CGG repeat in het FMR-1 gen) werd uitgevoerd in de groep patiënten met klinische kenmerken van het syndroom en/of met een positieve anamnese van familiale verstandelijke handicap (maternele MR). Metabool onderzoek werd systematisch verricht in 306 van de 471 onderzochte verstandelijk gehandicapte patiënten. Naast PKU en de klinisch herkenbare lysosomale stapelingsziekten, die voorheen reeds waren gediagnosticeerd, was de opbrengst van het metabool onderzoek in dit instituut gering. De ervaring in dit instituut leert dat screening naar metabole ziekten bij oudere geïnstitutionaliseerde volwassenen kan beperkt blijven tot die groep patiënten met neurodegeneratieve aandoeningen of gedragsproblemen. Ofschoon beeldvorming van de hersenen werd uitgevoerd in een kleine groep streng geselecteerde patiënten, werden weinig afwijkingen gevonden en was geen enkele diagnostisch.

In een tweede luik worden de medische en gedragsproblemen bij het verouderen in de algemene populatie verstandelijk gehandicapten besproken, evenals specifieke problemen gerelateerd aan de diagnose. De ernst van verstandelijke handicap speelt een belangrijke rol bij gezondheidsproblemen waarbij een hoger risico wordt gevonden bij ernstigere niveaus. Spasticiteit, visus en gehoorsverlies, motorische beperkingen, epilepsie, spraakproblemen, emotionele en/of mentale moeilijkheden worden vaak vermeld bij oudere verstandelijk gehandicapten en voegen een nieuwe dimensie toe aan het verouderingsproces. Deze problemen resulteren in een beperking van de sociale contacten en leiden vaak tot gedragsproblemen, zoals agressief gedrag en automutilatie, in de groep ernstig tot diep verstandelijk gehandicapten. Matig verstandelijk gehandicapten kunnen reageren met onaangepast gedrag en kunnen depressie ontwikkelen. Comorbiditeit is, afgezien

van het Down syndroom, weinig beschreven bij andere genetische syndromen. In dit instituut bestudeerden wij de medische en gedragsproblemen bij Down syndroom evenals bij andere groepen patiënten met een diagnose. Aanbevelingen werden geformuleerd voor de zorg bij verstandelijk gehandicapten.

In een addendum worden richtlijnen voor genetische onderzoeken bij volwassen verstandelijk gehandicapten geformuleerd.

CURRICULUM VITAE

Griet Van Buggenhout werd op 9 april 1963 geboren te Leuven, België. Het diploma Latijn-Wetenschappen werd behaald aan het Paridaensinstituut te Leuven. Het diploma van Doctor in de Genees-, heel- en verloskunde werd in 1989 behaald aan de Katholieke Universiteit te Leuven. In 1990 werden aan dezelfde universiteit het diploma van Geneesheer-hygiënist in de Jeugdgezondheidszorg, en het diploma van Geaggregeerde voor het HSO en HOKT voor Geneesheren, behaald. De attesten "Biostatistiek voor het wetenschappelijk onderzoek" en "Epidemiologie voor het wetenschappelijk onderzoek" werden in 1991-1992 behaald (KU Leuven). Van 1990 tot augustus 1992 was zij werkzaam als schoolarts verbonden aan het Medisch Schooltoezicht, achtereenvolgens te Halle, Mechelen en Gistel, en werkte zij tevens als consultatiebureau-arts in verschillende kinderkribben, waaronder één met speciale opvang voor kinderen met gehoorsproblemen, en consultatiebureaus voor het jonge kind (Kind en Gezin). Daarnaast was zij van 1990 tot 1994 leerkracht aan de leergangen voor sociale promotie in het Stedelijk Instituut voor Technisch Onderwijs te Mechelen in de studierichting Tolk voor Doven.

Van september 1992 tot augustus 1996 was zij verbonden als arts-assistent bij de sectie Klinische Genetica van de afdeling Anthropogenetica van het Universitair Medisch Centrum St Radboud te Nijmegen onder leiding van Dr. BCJ Hamel (Hoofd: Prof. Dr. HH Ropers). Op dat ogenblik werd onder meer aanvang gemaakt met het systematisch etiologisch onderzoek van een 600-tal bewoners van Huize Assisië - Stichting Prisma, een woon- en leefgemeenschap voor verstandelijk gehandicapten te Biezenmortel. De resultaten hiervan liggen ten grondslag aan dit proefschrift. Vanaf augustus 1994 is zij werkzaam als arts-klinisch medewerker, eerst deeltijds, en vanaf augustus 1996 voltijds, aan het Centrum voor Menselijke erfelijkheid onder leiding van Prof. Dr. Fryns te Leuven, België.

Daarnaast heeft zij een bijzondere interesse voor optica en pré-cinema en is sedert 1993 lid van twee Magic Lantern Societies (Londen en USA & Canada).

Griet Van Buggenhout is getrouwd met Stefaan Mulier en ze hebben samen 2 kinderen: Astrid (°5/11/1996) en Maarten (°8/10/1998).

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