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Visual performance in specific syndromes associated with intellectual disability

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PURPOSE. *To report visual performance in adults with specific causes of intellectual disability (ID) and to compare the test results to published reports.*
METHODS. *In a large-scale multicenter epidemiologic study of sensory impairments in 1598 adults with ID, the authors performed ocular assessments in 1539 persons. They compared the test results of those with five specific genetic disorders (Angelman syndrome, Prader-Willi syndrome, fragile X syndrome, Williams-Beuren syndrome, and tuberous sclerosis).*
RESULTS. *An overrepresentation of strabismus, low vision, and refractive errors was found. Apart from fragile X syndrome and Prader-Willi syndrome (with in general mild to moderate ID), the other syndrome groups contained one or more subjects with visual impairment or blindness. A number of them had never been seen by an ophthalmologist.*
CONCLUSIONS. *The authors confirm a number of ocular features previously reported by other studies and suggest some additional ocular features. They found increased frequencies of treatable ophthalmologic conditions in the subgroups. Because reliable ocular assessment is feasible for 85% of persons with ID, the results are an incentive to address visual functioning in people with ID in order to correct ocular problems and maximize their possibilities. (Eur J Ophthalmol 2003; 13: 566-74)*

KEY WORDS. *Angelman syndrome, Fragile X syndrome, Prader-Willi syndrome, Tuberous sclerosis, Visual impairment, Williams-Beuren syndrome*

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INTRODUCTION

The risk of people with intellectual disabilities (ID) being affected by visual impairment or other ophthalmologic problems is higher than in people without ID (1). The large population of adults with ID in our ongoing multicenter epidemiologic study on vision and hearing contained some small groups with the same diagnosed etiologic syndrome. The purpose of this article is to report the results of vision screening and ophthalmologic assessment in some of these groups with specific diagnoses. We chose syndromes that were represented by homogeneous groups. We deliberately did not focus on Down syndrome (DS), because of our earlier conclusion (2) that there already seems to be greater awareness of the risk of ophthalmologic problems in people with this syndrome and the fact that there are already many reports on the ocular features of DS. We selected the following other specific genetic disorders: Angelman syndrome, Prader-Willi syndrome, Fragile X syndrome, Williams-Beuren syndrome, and tuberous sclerosis.

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METHODS

The design of the Dutch multicenter study on vision and hearing screening in adults with ID has been described (2). In summary, from a background population of 9000 adults with ID (nearly 10% of the total Dutch population with ID (3)), a randomized sample of 2100 adults was drawn. Stratification was applied for age 50+ and DS, both risk factors for visual impairment. Stratification was applied to obtain subgroups large enough to yield valid information on subgroup prevalences and on relative risks. Subgroup sizes were based on prevalences of sensory impairment as known at the moment from a study among institutionalized adults with ID (4). We further increased the sample size of the group with age 50+ and DS, in order to anticipate expected losses due to dementia and early death. DS had been confirmed by karyotype examination in every case. Participants aged 18 years or older from institutions and daycare centres were included; the degree of intellectual ID varied from mild to profound. Informed consent was obtained from the participants or their legal representatives. The medical records were checked for documented cause and degree of ID (AAMR criteria (5)) and medical history. In all cases described in this article, the clinical diagnosis had been confirmed by cytogenetic or molecular assessments.

The ophthalmologic assessment was performed onsite by skilled investigators (skilled physician [J.v.S.] and orthoptists). The time reserved for each assessment was 45 minutes (2). The examination consisted of the following:

1. External observation of visual attention, fixation, position of the eyes (light reflex and motility testing), and external eye structures;
2. Visual acuity (VA) measurement consisting of one but preferably two of the following tests: Snellen chart (6), Burghart children's chart, STYCAR single characters and matching (7), Cardiff Acuity Cards (8), and Teller Acuity Cards (9). These methods assess either recognition acuity or pattern resolution acuity, which are not completely comparable (10). Because of statistical reasons explained elsewhere (2), we did not discriminate between different methods of visual assessment. In order to investigate the relation between ID and VA, we expressed and compared all acuity outcomes in Snellen equivalents (11). Visual impairment was diagnosed according to World Health Organization (WHO) criteria. Best-corrected results are presented. When a participant with a refractive error refused correction, the presenting VA was used. Cerebral visual impairment was defined as visual impairment in the absence of any ocular disorders and accompanied by brief fixation and following;
3. Assessment of the visual fields with the STYCAR graded balls confrontational method (12);
4. Hand-held slit-lamp biomicroscopy and tonometry with a Tono-Pen;
5. Refraction determined with the Nikon autorefractometer, type Retinomax K-plus, or by skiascopy. Because cycloplegic eyedrops had an adverse effect on cooperation in a pilot group of 20 participants, they were discontinued. In order to relax accommodation, the testing rooms were made as dark as possible. Ophthalmoscopy was no part of the screening because of the mentioned troubles with cycloplegic eyedrops and the absence of an ophthalmologist during the screening. Persons with newly found visual impairment and no ophthalmologic history were referred for specialized ophthalmologic assessment.

We selected the following most frequent, genetically proven, specific causes of ID: Angelman syndrome, Prader-Willi syndrome, Fragile X syndrome, Williams-Beuren syndrome, and tuberous sclerosis.

RESULTS

General

We performed a visual assessment on 1539 adults with ID. Apart from assessment of the ocular pressure (only possible in 26% of the participants), a complete assessment was possible in 1309 of the 1539 (85%). Ages varied from 20 to 88 years, with a mean age of 45.7 years. The identified causes of ID are shown in Table I. The relatively large number of people with DS is the result of stratification. In 980/1130 (87%) participants, the cause of the intellectual defect was unknown. The present subgroup consisted of 3 adults with Angelman syndrome, 8 with Prader-Willi syndrome, 15 with Fragile X syndrome, 4 with Williams-Beuren

TABLE I - CAUSES OF INTELLECTUAL DISABILITY (N=1539)

Cause	Number
Acquired brain damage	19
Angelman syndrome	3
Bardet-Biedl syndrome	1
Congenital hypothyroidism	6
CHARGE syndrome	1
Chromosomal deviations (unspecified)	10
Delleman syndrome	1
Down syndrome	409
Dystrophia myotonica	2
Encephalitis	
Unspecified	4
Post measles	4
Fragile X syndrome	15
Meningitis/meningoencephalitis	24
Microcephalia vera	1
Moebius syndrome	1
Mucopolysaccharidosis	3
Neonatal jaundice	5
Neurofibromatosis	1
Phenylketonuria	4
Prader-Willi syndrome	8
Prenatal rubella infection	2
Perinatal damage (including prematuritas)	19
Rubinstein-Taybi syndrome	2
Sturge-Weber	2
Toxoplasmosis	2
Tuberous sclerosis	5
Turner syndrome	1
Williams-Beuren syndrome	4
Unknown	980

CHARGE = Coloboma, Hearing deficit, Choanal atresia, Retardation of growth, Genital defects, and Endocardial cushion defect

syndrome, and 5 with tuberous sclerosis. We found a high prevalence of various specific ocular abnormalities in the subgroup as a whole. Of the 35 people with the selected five specific causes of ID, 16 had a refractive error, 14 had strabismus, and 5 had visual impairment or were blind. Ocular pressure could be reliably measured in 16, none of whom had a pressure >21 mm Hg. Information from retinal examinations by ophthalmologists was available for 26 persons. Seven had not been assessed previously and were not referred because of their normal screening results, whereas in two cases the ophthalmologist failed to perform ophthalmoscopy owing to lack of cooperation of the patient.

Angelman syndrome

Specification. Cytogenetically visible deletions of the long arm of chromosome 15, which were first associated with Prader-Willi syndrome, are also reported in 50 to 80% of patients with Angelman syndrome. Both syndromes are associated with deletions of chromosome 15q11-13, of maternal origin in Angelman syndrome and paternal in Prader-Willi (13-16). Clinically, the syndrome is characterized by a distinct pattern of anomalies including microbrachycephaly, a low forehead, macrostomia, and prominent mandible; postnatal growth deficiency; severe to profound ID, mostly without speech development; ataxia; jerky movements; hand flapping; tongue thrusting; unmotivated outbursts of laughter; and epilepsy (17, 18). Ocular features mentioned are refractive errors (usually hyperopia), strabismus, iris and choroid hypopigmentation, and optic atrophy (19).

Findings. In the present population, three participants (age range 44 to 51 years), including two women, had been identified with this syndrome, all with a severe to profound ID. All three were or had been under the supervision of an ophthalmologist, who had diagnosed low vision. Assessment of best-corrected VA proved impossible, because all three of them refused to be assessed with spectacles. All three had severe refractive errors and hypopigmentation of the iris; strabismus was found in two. Fundus examination revealed optic atrophy in one and no fundus abnormalities in the other two persons (Tab. II).

Prader-Willi syndrome

Specification. Cytogenetic causes were described above. Clinical features include infantile hypotonia, hypogonadism, obesity after infancy, mild to moderate intellectual disability, characteristic dysmorphic facial features, and short stature. Other features include small hands and feet, skin picking, and behavioral problems. Hered et al (20) have performed one of the very few larger studies (46 children and adults)

TABLE II - OCULAR FINDINGS IN CASES WITH SPECIFIC CAUSES OF INTELLECTUAL DISABILITY (N=35)

Characteristics	AS	PWS	FXS	WBS	TS	Total
Number of participants	3	8	15	4	5	35
Mean age, yr	47.0	40.4	43.9	41.5	41.2	42.7
Best-corrected visual acuity						
≥0.3	0	7	15	3	4	29
<0.3, ≥0.05	2	0	0	1	1	4
<0.05	1	0	0	0	0	1
Assessment failed	0	1	0	0	0	1
Amblyopia	0	1	1	0	0	2
Refractive measurement						
Emmetropia	0	2	5	2	1	10
Myopia*	2	2	3	1	1	9
Hypermetropia*	1	1	4	1	0	7
Assessment failed	0	3	3	0	3	9
Astigmatism > 1.00	0	3	6	0	0	9
Cataract	0	1	3	1	0	5
Coloboma	0	0	0	0	0	0
Microphthalmos	0	0	0	0	0	0
Nystagmus	0	1	0	0	0	1
Strabismus	2	6	4	1	1	14
Assessment failed	3	5	6	1	4	19
Keratoconus	0	0	0	0	1	1
Retinal anomalies	1	1	0	0	2	4
No information	0	0	5	1	3	9

*Refractive error > ± 1.00 diopters;
AS = Angelman syndrome; PWS = Prader-Willi syndrome; FXS = Fragile X syndrome; WBS = Williams-Beuren syndrome; TS = Tuberous sclerosis

on ophthalmologic features of the Prader-Willi syndrome. They found the most prevalent ocular feature to be strabismus: 48% had esotropia and 7% had exotropia. Iris hypopigmentation was often found, as were moderate reduced VA, amblyopia, refractive errors, and astigmatism. Other studies, mostly case reports (21-25), reported the same ocular features.

Findings. In the present population, eight participants (age range 23 to 69 years), including three women, were identified with the syndrome. Five of them had a mild to moderate ID, two a severe ID, and one a profound ID. All of them had been under the supervision of an ophthalmologist since childhood. One had previously had severe myopia (S-16 diopters in both eyes). However, a few months before our investigation, he had undergone cataract surgery with insertion of intraocular lenses, and was now assessed without spectacles. One 35-year-old man with profound ID shut his eyes and refused all cooperation with the assessment. He was referred to an ophthalmologist who, after sedating the patient, found slight esotropia of his left eye, but no other significant anomalies. In the other participants it was possible to assess the best-corrected VA. One participant had both retinal and corneal scars of the right eye resulting in amblyopia, due to congenital toxoplasmosis. We therefore were not able to assess the refractive error of this eye. The others with refractive errors all had accurate correction. Three of the seven participants who could be assessed had iris hypopigmentation. Detailed results are presented in Table II.

Fragile X syndrome

Specification. The etiology of this syndrome is an enhanced CGG repeat in the FMR1 gene on the X-chromosome (26). Typical clinical features are macroorchidism, large/prominent ears, and a long, narrow face. Clinical features are often more obvious in males than in females. Most patients are mildly to severely intellectually disabled. Frequent ocular disorders mentioned in combination with this genetic disorder are high refractive errors, strabismus, and nystagmus (27-29). Less frequently, astigmatism and adult-onset glaucoma were found. No major visual loss has been associated with fragile X syndrome.

Findings. Fifteen adults in the present population had a diagnosis of fragile X syndrome (14 men, 1 woman); two had a severe ID and the rest a mild to moderate ID. Age range was 27 to 60 years. All 15 had normal vision: astigmatism was found in 6 and strabismus in 4 participants. Three refused assessment of monocular VA, making identification of amblyopia impossible. Five participants had never visited an ophthalmologist and because they had no visual impairment, they were not referred after the present screening. The retinal information of the others showed no abnormalities (Tab. II).

Williams-Beuren syndrome

Specification. Williams-Beuren syndrome appears to be associated with the deletion of a region on chromosome 7, including the area around the elastin gene and other identified genes (30, 31). Clinical features are typical facial features ("elfin face") with short palpebral fissures, medial eyebrow flare and thick lips, supravalvular aortic stenosis, abnormal calcium metabolism, and variable ID (32-34). Ocular disorders mentioned are iris abnormalities (stellate iris), small optic nerves, retinal vascular abnormalities, and strabismus (35).

Findings. In the study population, four adults (age range 28 to 55 years), including one woman, had an established diagnosis of this syndrome. Each underwent the complete assessment without any problems. Three of them had moderate and one severe ID. Two had been assessed by an ophthalmologist previously. One of the participants had strabismus; another had received strabismus surgery in the past. All four had stellate irides. One had the characteristics of cerebral visual impairment; the other three had an accurately corrected refractive error. Retinal information revealed no anomalies (Tab. II).

Tuberous sclerosis

Specification. Tuberous sclerosis is a genetically heterogeneous disease. The gene is located on chromosome 9q (36) and chromosome 16p (37). Mild to profound ID occurs in 50 to 60% of patients (38, 39). The clinical manifestations of this hereditary disorder are related to the presence of hamartias and their progression to hamartomas in one or more organs, notably the skin, central nervous system (including the retina), kidneys and heart. The clinical spectrum is therefore very diverse and variable. Ophthalmologically, the retinal hamartomas are the most prominent lesion; other reported ocular lesions are alterations in retinal pigment, strabismus, coloboma of the iris, tumors of the lid and conjunctiva, and hamartomas of the optic disc (40).

Findings. Assessment of the five participants with the diagnosis of tuberous sclerosis was difficult (Tab. II). The group consisted of one woman and four men (age range 29 to 53 years). Four of them had profound ID, and the other was severely intellectually disabled. One did not cooperate with monocular VA assessment at all. It was only possible to determine the refractive error exactly in one case; in three cases it was impossible and in one case cooperation was just enough for a rough estimate. Therefore, it was impossible to optimize the VA. Two of the participants with this cause of ID had been to an ophthalmologist previously. One had optic atrophy and retinal hamartomas; the other had keratoconus and optic disc hamartomas. Of the other three, one was not referred. The other two were uncooperative during assessment by the ophthalmologist, so ophthalmoscopy was impossible.

DISCUSSION

In the present study, the diagnostic categories were represented by relatively small numbers of identified cases. Because a low rate of identified causes of ID is universal, this might explain the fact that published studies on syndrome-specific ophthalmologic features have been scarce and descriptive. In spite of the rapidly growing knowledge on etiologies of ID, in practice, the cause of ID has not been diagnosed in a majority of adults. In our study population, if we exclude DS, the cause was only known in 150/1130 (13%) participants. Other authors (41-44) have obtained percentages for etiologic diagnoses varying between 32 and 80, but most of these figures relate to children.

General

The estimated prevalence of visual impairment in the general adult population younger than 55 years in the Netherlands, based on two inventories (45, 46), is between 0.2 and 0.8 to 1.9%. For people over 55 years of age, this prevalence is 0.8% for men and 1.9% for women (47). The prevalence of 5/34 (15%) found in the present group with five specific syndromes is thus substantially higher. Some of the ocular abnormalities we found within these syndromes have been described previously; others were newly found. Apart from visual impairment, 14/35 (40%) had strabismus, which is also substantially higher than internationally published prevalences in the general population (4 to 7%) (48-51). Refractive errors were found

in 16/26 (62%), compared to 55% in a group of army recruits (52). Ocular pressure assessment was reliably possible in less than half of the participants and did not reveal any abnormalities.

Angelman syndrome

Dickinson et al (17), Schneider and Maino (18), and Mah et al (19), in three small series (one to eight patients), found the most prevalent ocular findings in Angelman syndrome to be iris and choroid hypopigmentation, strabismus, and refractive error. In our population, all three adults with Angelman syndrome had hypopigmentation of the iris, two of the three had esotropia, and all three had a severe refractive error. Two of the three, however, had severe myopia instead of the hyperopia found by the former investigators. Furthermore, Dickinson et al (17), Schneider and Maino (18), and Mah et al (19) concluded that optic atrophy, which was originally described by Angelman as one of the characteristics of the syndrome, was rarely found. It is interesting to note that one of our participants who did have optic atrophy also had a hearing impairment. The child originally reported by Angelman had the same combination of impairments, but after Angelman's report, only one other patient with the syndrome has been reported (53) with this same combination. Because the prevalence of strabismus and refractive error is high for many other causes of ID, these anomalies may not be syndrome-specific ocular features for Angelman syndrome. The characteristic iris hypopigmentation is also seen in Prader-Willi syndrome.

Prader-Willi syndrome

We confirm the finding of Hered et al (20) and others of a high frequency of strabismus, iris hypopigmentation, and astigmatism. However, we found amblyopia in only one of our participants. The moderate reduced VA mentioned by Hered et al (20) was not defined according to WHO classifications. In fact, only one of their patients had visual impairment. We agree with their finding about the unwillingness to wear glasses: three of our participants did not even cooperate with assessment of their refraction. As with Angelman syndrome, the iris hypopigmentation appears to be the only syndrome-specific ocular feature.

Fragile X syndrome

Similar to reports by former authors (27-29), the best-corrected VA of all 15 participants with this syndrome in the present study was higher than 0.3. We did not find any high refractive error (>5.0 diopters), but comparison of this item with the results of Maino et al (27-29) is difficult, because they did not define their terms. We found astigmatism in six of the seven adults with refractive errors. Four of our participants had strabismus. Three participants with cataract were between 54 and 57 years of age. Early development of cataract may be an as yet unreported feature of fragile X syndrome. Otherwise, we consider none of the above-mentioned ocular features to be specific for this syndrome.

Williams-Beuren syndrome

The most prominent ocular features reported (34, 35, 54)–namely, strabismus and the typical stellate pattern of the iris–were also found in our four participants identified with this syndrome. All of the present participants with this syndrome had the typical iris anomaly and two of the four had strabismus. The typical elfin-face (lid and palpebral abnormalities) in Williams-Beuren syndrome makes it difficult to judge the existence of strabismus. We tried to overcome this by assessing the position of the eyes with light reflexes and motility tests. We did not find any ocular signs of abnormal calcium metabolism, such as calcium deposits in the conjunctiva or opacities in the lens (55). No visual impairment is reported in the literature. One of our participants, however, a 37-year-old man with severe ID, had a visual acuity of 0.2. His ophthalmologist had diagnosed a cerebral visual impairment years ago.

Tuberous sclerosis

Because ophthalmoscopy was not performed in one and not possible in two other participants, information about the retina was available for only two participants with this cause of ID. Anterior segment findings mentioned in the literature, such as iris abnormalities, atypical coloboma, angiofibromas of the lids, and poliosis, are reported to be rare (56). Optic atrophy, papilledema, and strabismus have also been re-

ported (57, 58). Dotan et al (59) suggest that visual impairment is unusual in tuberous sclerosis. It only occurs if a retinal hamartoma involves the macula, or as the result of optic nerve damage secondary to chronic papilledema, caused by raised intracranial pressure. One of our participants was known to have optic atrophy. Another had been diagnosed as socially blind years before this study. He had the retinal complications of tuberous sclerosis and keratoconus. Keratoconus as a complication of tuberous sclerosis has not been reported before.

CONCLUSIONS

This study showed a wide spectrum of ocular abnormalities in persons with different causes of ID. Increased frequencies of visual impairment, and correctable ophthalmologic diagnoses like refractive errors and strabismus, were found in the group as a whole. In these participants with identified causes of ID, we found new anomalies. Treatment of correctable causes such as refractive errors and strabismus at a young age may have a positive effect on the development, whereas early treatment of age-related ocular features like cataract may prevent functional decline. We found that 85% of the population is reliably assessable; therefore, the present results may be an incentive to assess visual functioning in all people with ID in order to maximize their care.

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