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OCULAR ASSESSMENT
OF THE AGING DOWN'S SYNDROME PATIENT

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ABSTRACT

Down's syndrome, a chromosomal disorder, results from the fetus receiving a triple amount of a band on the long arm of chromosome 21. The incidence of Down's syndrome births has decreased, but the prevalence of older Down's syndrome individuals has increased. Aging appears to occur earlier and progress faster in Down's syndrome than in the general population. Unique early aging changes have been found to occur in the immune, endocrine and neural systems. Neuropathological changes that resemble Alzheimer's disease occur in almost all Down's syndrome individuals by age 40. Common ocular problems in Down's syndrome are moderate refractive error, esotropia and blepharitis. High myopia, keratoconus and nystagmus are more frequent than in the general population.
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INTRODUCTION

Aging is a universal process. This process is variable in normals, but in Down's syndrome, individuals undergo some aging changes that are uniquely different than normals. They also seem to have a different timetable to their aging changes. It is currently felt that aging occurs earlier and progresses faster in Down's syndrome. For instance, a 45 year old Down's syndrome individual will commonly exhibit aging changes normally not present until 65 years of age in normals. Maximum recorded life span for a Down's syndrome individual is approximately 71 years old.1

The health care practitioner must keep in mind special considerations when working with the Down's syndrome patient. They are born with a genetic alteration which can impact any of the organ systems of the body. As Down's syndrome patients increase in age, some unique considerations must be kept in mind. As members of the health care team, optometrists have a professional obligation to be competent in handling these patients. Although Down's syndrome is relatively rare, chances are good that an optometrist in every community will be called on to care for a Down's syndrome individual. The following material is a review of the important Down's syndrome considerations, with a special emphasis on aging.
HISTORY

In 1866 Langdon Down was the first to ascribe the unfortunate term "mongolism" to those with mental deficiency, short stature and mongolian features. He was attempting to use ethnic background as a means of categorizing the mentally retarded. Down, himself, questioned his own findings because the disease seemed to cross ethnic barriers. At first mongolism was frequently confused with cretinism. Subsequently, workers differentiated Down's syndrome to be a distinct entity. The first documentation of ocular findings for mongolism occurred in 1891 (Oliver). It wasn't until 1959 that the true etiology of Down's syndrome was advanced with the recognition that those with Down's syndrome have 47 chromosomes.

GENETICS OF DOWN'S SYNDROME

Down's syndrome is a chromosomal disorder resulting from a triple amount of the critical chromosomal band 21 q 22. This band which results in the phenotype of Down's syndrome is part of the long arm of chromosome 21. Triplication of this critical portion can result from three different genetic alterations. 96% of the cases result from complete trisomy 21 and is caused by nondisjunction in either parent. The chromosome count in this condition is 47. It is one of the few trisomies, which is allowed by nature to come to full term. 3% of the cases result from unbalanced translocations, usually to the D and G chromosomal groups. Chromosome count here is 46 and these cases tend to be familial. Mosaics account for about 1% of Down's syndrome. These cases are a result of mitotic nondisjunction of chromosome 21 in an early stage of
embryogenesis. Their cells contain either 46 or 47 chromosomes. Depending on the stage at which embryogenesis was affected, these individuals can be either mildly or more severely affected.

It is estimated that chromosome 21 represents less than 2% of the human genome of approximately 100,000 genes. Chromosome 21 is estimated to contain less than 1,000 genes with the portion 21 q 22, itself having an estimate of less than 100 genes. This small gene pool which is responsible for the phenotype in Down's syndrome has lead some researchers to feel that most of these genes are regulatory involved rather than structural. At this time only five genes have been mapped to chromosome 21. One of these is for cytoplasmic superoxide dismutase, an enzyme which has been known to have a dosage effect in Down's syndrome. Some interferon regulation has also been mapped to here.

CHARACTERISTICS OF DOWN'S SYNDROME

There are a number of diagnostic clinical features which are commonly found in this syndrome. The unfortunate term "mongolism" resulted from the flat facial profile, oblique palpebral fissures and epicanthic folds. Varying skeletal anomalies are present such as short limbs, broad and short trunk, broad hands, small nose, depressed nasal bridge and dysplastic pelvis. Additional signs are muscle hypotonia, hyperflexibility, dysplastic ears and transverse palmer crease. Congenital heart disease occurs in about 30% of Down's syndrome newborns; usually it is a ventricular septal defect. Males are usually sterile; females may be fertile. Duodenal atresia is also known to occur.

The mental retardation occurring in Down's syndrome is felt to be
severe to moderate in range with about 80% having an I.Q. between 25 to 50. Studies have shown that the introduction of special developmental programs can increase intellectual abilities in a portion of the Down's syndrome population.

INCIDENCE AND PREVALENCE OF DOWN'S SYNDROME

The incidence of Down's syndrome is strongly influenced by maternal age. The risk of bearing a child with Down's syndrome is 1 in 2,000 at age 20 years. The risk rises gradually until at age 35 where the risk increases to 1 in 300. By age 45 years, the risk has risen to 1 in 45. The cause of the mitotic nondisjunction in the ova is not presently known, but since the ova are present from birth, environmental factors may influence this. Recent studies have shown that in 20% of the cases the extra chromosome is from the father. No conclusions have yet been reached concerning whether paternal age has an influence on the incidence of Down's syndrome.

Maternal bearing age and use of prenatal diagnosis seem to be the two primary factors influencing the crude incidence of Down's syndrome births. Between the years of 1960 and 1978 there was a substantial decrease in Down's syndrome births. Crude incidence shifted from 1.33/1,000 births in 1960 to .99/1,000 births in 1978. It is felt that most of this decrease was due to a 50 percent reduction of women 35 years of age and over giving birth. Decreased maternal bearing age and reduction in the total number of births in the United States accounted for most of this change. Maternal bearing age distributions changed by the year 1978 such that women over 35 accounted for only 20% of all Down's syndrome
births.\textsuperscript{13}

In 1970 the medical community felt that it was economically justifiable to try to make prenatal diagnosis available to all mothers older than age 35. The rational behind this, at this time, was that women 35 years and older had only 13\% of all pregnancies, but delivered 50\% of all Down's syndrome births.\textsuperscript{13} Prenatal diagnosis involves the removal of amniotic fluid from the mother after the twelfth week of pregnancy.\textsuperscript{14} Usually it is cells from the fetal skin which are analyzed. It is estimated that for each 10\% increase in the utilization rate of prenatal diagnosis by mothers over the age of 35, one can expect a 3.5\% drop in the overall Down's syndrome live birth rate.\textsuperscript{15} Risks of prenatal diagnosis are low being between 1 and .3\%.\textsuperscript{13} Usual complications are vaginal bleeding and amniotic fluid leakage. Current usage by women over age 35 is at about 17\%.

Given current prenatal diagnosis rates, projections for the future predict an increase in Down's syndrome births from 4,300 in 1979 to 5,300 in 1990.\textsuperscript{16} The reason for this projected increase is that the age 35 to 49 category will rise from a 1980 level of 19 million to about 30 million by 1995. Another factor may be the trend towards increased mean maternal child bearing age.

There has been a marked increase in the prevalence of older Down's syndrome patients during the past decade.\textsuperscript{17} There are a number of reasons for their increased survival. Increased effort, interest and technology have improved the one year survival rate from an estimate of 50\% prior to the year 1950 to about 94\% in 1984. Improved surgical techniques have reduced the one year mortality ratio for congenital heart disease patients to less than 13\%. It is now felt that 82.4\% of Down's
syndrome children survive the first 10 years of life.\textsuperscript{18}

Quality of life has improved significantly for the Down's syndrome individual. Significant improvements have been made in the diagnostic, therapeutic and educational skills necessary to help these individuals.\textsuperscript{17} An important improvement has been the recent trend towards deinstitutionalization. This has resulted in increased stimulation and mobility, earlier intervention into the problems inherent with Down's syndrome and more careful attention to diet and fitness. Reliable life-tables indicate that it is not unusual for Down's syndrome people to reach 44, with 60+ not being exceptional.

**AGING CHANGES IN DOWN'S SYNDROME**

In the past there have been many citations in the literature indicating that people with Down's syndrome tend to age prematurely. The aging process is also felt to progress faster than in the general population. The recent increase in longevity of the Down's syndrome patient has resulted in renewed interest in this area.

Researchers have found a variety of evidence to support the premature aging theory. Down's persons tend to appear older than their actual age.\textsuperscript{9} This is due to premature greyness, absence of hair and dryness of the skin.\textsuperscript{19,20} In one study aortic and pulmonary valve funestrations were found in 50\% of a Down's syndrome group as compared to only 4\% of the controls.\textsuperscript{21} Cataracts tend to form earlier in the lens of Down's patients.\textsuperscript{22} The skeletal system tends to show some rapid aging changes.\textsuperscript{23,24} Postural changes that usually appear in the fifth or sixth decade of life have been found in the third decade.\textsuperscript{25} Early menopause and
testicular atrophy have also been found.26

An increase in the oxidative enzyme superoxide dismutase (SOD) has been dosage linked to Down's syndrome.23 This enzyme has been genetically mapped to the long arm of chromosome 21. It is responsible for the oxidative process with the cell ultimately resulting in the hydroxyl radical. Excess dosage of SOD may lead to cell damage and thus be a part of the aging process.

For a long time, the immune status of Down's syndrome patients has been under investigation. Respiratory infections are 100 times more common in Down's syndrome children as compared to age matched controls.27 Down's individuals have a high frequency of malignancies, especially leukemia which is 20 times the normal rate.28,29 There is also an increased prevalence of anti-thyroid antibodies.30 Mortality from infectious disease is high.31 Down's syndrome has also been associated with a high incidence of chronic carrier state for Australian antigen.

Immunodeficiency seems to be an integral feature of Down's syndrome. There have been reports of slight B-cell system irregularities, but the preponderance of current evidence seems to point towards the T-cell system.29 It appears that changes occur in the thymic epithelial cells which results in a failure to secrete the necessary hormones to stimulate T-cell differentiation. Histologic changes noted in the Down's syndrome thymus include lymphocyte depletion, diminution of the cortex of the lobules and degeneration of the Hassall corpuscles.27 Newborns with Down's syndrome already have present a degeneration of the Hassall corpuscles which are felt to be a morphologic Index of the function of thymic epithelial cells. Lymphocyte depletion has been noted in the T-cell zones of the spleens and lymph glands of Down's syndrome patients.
Failure of T-cell differentiation may be a key factor in the early appearance of autoantibodies in Down's syndrome. They may also play a role in the lymphoid malignancies. The recurrent infections common in Down's syndrome may stress an already deficient immune system and thus tend to exhaust the system. Institutionalization with its high rate of recurrent infections, would be an important accelerating factor if this were true.

There is an increased prevalence of thyroid disorder in Down's syndrome, but studies concerning thyroid function have been conflicting. One study found an overall prevalence of thyroid dysfunction to be 19.5%. In this study hypothyroidism was found in 17%, hyperthyroidism in 2.5% and 18% of the patients had goiter. Thyroid antibodies were found in 33% of the subjects. Most of the abnormal thyroid function was shown to be in adolescents and young adults.

A number of neurological changes are characteristic for the aging Down's syndrome patient. There have been reports of age related changes in the EEG. An increased frequency of late onset epilepsy has been noted. The visual, auditory and somatosensory evoked responses have a larger late wave component in Down's syndrome as compared to normal. Thus Down's syndrome subjects can be characterized as lacking central inhibitory components. Usually in normals the late wave components decrease with aging, but this change does not occur in Down's syndrome.

The neurological change of most interest today is the Alzheimer's disease-like dementia which frequently occurs in many older Down's syndrome patients. The first notation of a dementia occurring in Down's syndrome occurred over 100 years ago. In recent years a vast amount of research has attempted to establish a relationship between Alzheimer's
disease and Down's syndrome.

Alzheimer's disease is a form of dementia that is felt to affect over two million Americans. More than 60 disorders can cause the symptom complex, termed dementia. Alzheimer's disease accounts for 50 to 60% of these cases. This condition is considered to be age dependent with incidence rising markedly in the 75 to 85 age group.

Presently there is no peripheral biochemical marker known for Alzheimer's disease. A cerebral biopsy must be performed in order to obtain a definitive diagnosis. The principle morphological changes in the brain are cortical atrophy, loss of neurons and the presence of neurofibrillary tangles, neuritic plaques and amyloid deposits. Neurofibrillary tangles are abnormal neurons whose cytoplasm is filled with microscopic helically wound filamentary structures. Neuritic plaques are clusters of degenerating nerve terminals. There is felt to be a correlation between the number of these lesions and the degree of the dementia. The neurotransmitters felt to be most lacking in Alzheimer's disease is acetylcholine and choline acetyltransferase. Known risk factors for the disease are age, history of serious head trauma, occurrence in a parent of sibling and presence of trisomy 21. Researchers are uncertain whether Alzheimer's disease is a biochemical deficiency, an infectious process, a toxic condition or an acceleration of normal aging.

The dementia that occurs in Down's syndrome usually is not present before age 40 years. By age 40 nearly 100% of the Down's syndrome population have the neuropathologic plaques and tangles that are characteristic of Alzheimer's disease, but only 25 to 40% become demented. There is some evidence that Down's syndrome individuals invariably experience declining mental abilities as they age. Older Down's
patients in general tend to perform poorer on tests of attention, visual memory and intelligence. The dementia which occurs in older Down's patients is characterized by changes in behavior, loss of self care skills and deterioration in the use and understanding of language. Affected Down's syndrome brains show a reported reduction in the enzymes choline acetyltransferase and acetylcholine esterase. Dementia is not inevitable for all aging Down's patients, but a considerable number do have this problem.

A number of interesting models have been advanced in an attempt to establish a relationship between Alzheimer's disease and Down's syndrome. Mozer, et. al. suspect that Down's syndrome is a congenital form of Alzheimer's disease and that both conditions are the result of a ubiquitous infective pathogen that affects genetically susceptible individuals. An atypical virus may be present in a parent which would result in the nondisjunction causing Down's syndrome. The virus would then persist in the fetus and eventually lead to Alzheimer's disease in long-time survivors. No virus has as yet been isolated for Alzheimer's disease, but Alzheimer's disease does have similarities to the transmissible encephalopathies.

Schweber has suggested a unitary genetic hypothesis for Alzheimer's disease and Down's syndrome. This theory holds that Alzheimer's disease and Down's syndrome form a continuum. The theory here is that Alzheimer's disease results from a tripling of a subsection of the critical segment (21 q 22) which is responsible for the phenotype in Down's syndrome. Support for this theory lies in the fact that Down's syndrome is more common in families of Alzheimer's patients.
OCULAR FEATURES OF DOWN'S SYNDROME

The mentally retarded tend to have a higher frequency of ocular anomalies than the general population.\textsuperscript{42,43} Down's patients also tend to have a high frequency of ocular anomalies, but they also tend to have some uniquely different presentations.

External ocular findings that are commonly found in Down's syndrome are epicanthus, oblique upward and outward slanting palpebral fissures, and narrowed interpupillary distance. Jaeger\textsuperscript{3} found epicanthus in 17.3\% whereas Gaynon and Schimek\textsuperscript{44} found it to be present in 53\%. Variability in estimates of epicanthus may result from lack of a common definition. Also, some researchers feel that epicanthus prevalence may diminish by adolescence.\textsuperscript{45} The palpebral aperatures in Down's syndrome tend to be oblique and short. Lowe\textsuperscript{46} found the orbital axes to be inclined at 75 degrees as compared to the norm of 45 degrees. During growth the increase in interpupillary distance may lag behind the changes in skull breadth.\textsuperscript{47} This results in the eyes appearing set abnormally close together.

Refractive error tends to be significant in Down's syndrome. Jaeger\textsuperscript{3} used a criteria level of refractive error ($\geq \pm 4.00$ diopters of sphere or $-2.50$ diopters of cylinder) to judge his Down's syndrome subjects. 53.5\% of them exceeded this level and the refractive error seemed to be evenly distributed between myopia, hyperopia and astigmatism. Using a different criteria level of ($\geq \pm 8.00$ diopters of sphere or $-5.00$ diopters of cylinder) 16.9\% of the Down's subjects exceeded this level. Myopia was the predominant refractive error in this category. Other studies have also found a significant amount of high myopia to be present in Down's
Strabismus is commonly found in Down's syndrome. Estimates of the amount of strabismus range between 32\(^3\) to 41.3\(^3\) with esotropia being the predominant form. Hiles et al\(^5\) found 34% of their patients to be strabismic with 28% being esotropes. About half of the esotropes were felt to be accommodative esotropes.

Keratoconus is felt to have an incidence in Down's syndrome of about 5.5 to 8%.\(^5\) There have been many reports of acute hydrops occurring in patients with Down's syndrome.\(^5\) Acute hydrops is rare in normal keratoconus patients. Eye rubbing or trauma may be associated with this. Cullen found acute keratoconus to be one of the leading causes of blindness in Down's syndrome.\(^5\)

Lens opacities in Down's syndrome tend to occur earlier than in the general population and they also tend to be progressive.\(^3\) Lens opacities are rare in Down's syndrome children, but they have a dramatic rise in frequency after puberty. It is difficult to compare various studies of lens opacities in Down's syndrome because the descriptive terminology varies so much. Estimates of incidence of lens opacities range between 25 to 60%. Jaeger found 55.4% of his Down's syndrome subjects to have lens opacities. 36.5% of the subjects had flake-like opacities with the average age of presentation being 36 years. 18.9% of the patients had senile cataracts with average age of presentation being 48.

Early failure of accommodative ability in Down's syndrome children has been cited in one preliminary report.\(^5\) This was the only reference to this problem that was found in the literature. Further work needs to be done in order to explore this possible problem. No mention was made in this study of the type of drugs that these children were taking.
Considering the many health problems of Down's syndrome children and the large number of drugs which affect accommodative ability, this factor should be considered.

Nystagmus has been noted in Down's syndrome. Study incidences noted were 9%\textsuperscript{48} and 16%\textsuperscript{49}

Bleparitis has a high incidence of occurrence in Down's syndrome. Estimates of 46\textsuperscript{48} and 38\textsuperscript{49} have been made.

In Down's syndrome the ocular anomalies which occur tend to be composed of a variety of hyperplasias, hypoplasias, hamartomata, tissue defects and heterotopias\textsuperscript{58,59} All tissues except the vitreous have been shown to exhibit these various abnormalities. Most of the variations from normal are minor, and no variation has been found that does not occasionally occur in the general population. Thus, there is no "Down's Syndrome Eye." Hypoplasias and small tissue defects tend to be found in Descemet's membrane, corneal endothelium, iris stroma and retinal pigment epithelium. Heterotopias tend to occur in the lacrimal gland and iris pigment epithelium. Hyperplasias or hamartomata have been found in the conjunctiva, cornea, sclera, uvea and retina.

The iris in Down's syndrome can be characterized by Brushfield spots, peripheral iris stromal thinning, and a tendency towards blue or grey irides. Donaldson\textsuperscript{60} reported Brushfield spots in 85% and peripheral stromal thinning in 81% of his Down's syndrome patients. Brushfield spots are peripheral iris speckles which are felt to be made up of aggregates of stromal fibers. They are .1 to 1 mm in size and tend to have areas of decreased stromal fibers surrounding them.\textsuperscript{61} Shapiro and France\textsuperscript{48} found blue or grey irides in 87% of their Down's syndrome subjects.

The fundus in Down's syndrome individuals is felt to have similar
coloration to that of a blond. Despite refractive error or skin coloration, a decrease in pigmentation is noted in the Down's syndrome fundus. The fovea tends to be light colored and indistinct. The disc tends to appear rosy and it has been determined that an increased number of vessels leave it. It is common to see peripapillary and pigment epithelial cell atrophy. Peripheral cystoid degeneration is common. Characteristic fundus patterns occur in those with high myopia. Retinal detachments are felt to be more common in Down's syndrome. This may be due to the increased trauma which may commonly occur in their lifestyle.

CONCLUSION

The mental retardation in Down's syndrome has been described as being severe to moderate in range. Special educators have found that environmental improvements can result in substantial increases in the performance level of these patients. By providing quality vision care to individuals with Down's syndrome, optometrists can do a lot to enhance their lifestyle. These individuals will be special patients. They will require an understanding of their many disabilities. Special considerations will have to be kept in mind, such as their uniquely different aging process. The improvement made may be small, but, professionally, it can be very satisfying to help enhance the already limited lifestyle of the mentally disabled.
References


