Sistema nazionale per le linee guida

Management of congenital aniridia

GUIDELINES

Ministero della Salute

Note to readers

Guidelines permit the translation into clinical practice of knowledge from biomedical and sociomedical research. They represent the synthesis of systematic review of the scientific literature and expert opinion on the subject. As such, they provide a useful tool for physicians, researchers in clinical and basic science, professionals working in public health and social care, patients and their families, with a view to update knowledge, improve the quality of care, the coordination of actions and related policies and planning.

The application of guidelines recommendations resides within the area of competence of the health and social care provider, the patients and their family, who must take collaborative decisions, weighing the available scientific knowledge, the natural history of the disorder, and the patient's needs.

The low incidence of rare diseases makes it inherently difficult to conduct epidemiological and clinical trials sufficiently powered to provide evidence that can support guidelines recommendations regarding, for example, specific diagnostic procedures, alternative therapeutic strategies or certain social and health care interventions. This leads to heterogeneous decisions that ensue from deep clinical and organizational uncertainty.

Hence, the rationale for guidelines development in rare diseases cannot be based on available scientific evidence alone, but must also include the motivated and shared opinions of a multidisciplinary expert panel that takes part in drawing up these documents.

The international consensus on guidelines development methodology is that a document of recommendations based on expert opinion is to be considered a set of guidelines with a weak level of evidence. We, however, believe that, precisely because scientific information supported by high levels of evidence is lacking in rare diseases, guidelines can provide a useful instrument for ensuring clinical appropriateness and equity of care.

In light of the epidemiology of rare diseases, their complexity, and the limitations to conducting randomized trials in such patients (considered as higher levels of evidence), the development of guidelines in rare diseases, when done and shared by experts in a given rare disease – by those who attend patients with the disease and assist their families – actually brings them a unique strength and moves them toward application.

GUIDELINES

Management of congenital aniridia

This work is dedicated to the memory
of Professor Pasquale Vadalà.

The translated text in this document is the accurate and complete English translation of the original Italian document *Gestione dell'aniridia congenita*, published in April 2013 by the Centro Nazionale Malattie Rare – Istituto Superiore di Sanità (CNMR – ISS), in collaboration with the Sistema Nazionale per le Linee Guida (SNLG - ISS) available at: http://www.snlg-iss.it/lgmr_aniridia_congenita

Translated by Kenneth Adolf Britsch

Aniridia Italiana warmly thanks Silvia Cappelletto, a young designer who generously donated her time and skills to edit the English version of this document.

Foreword

With this publication, the National Center for Rare Diseases of the Istituto Superiore di Sanità presents a new set of guidelines for appropriate care for persons with congenital aniridia. Because it is a rare condition, currently available information about congenital aniridia must be collected, validated, and disseminated to patients and healthcare providers so as to provide them with the most recent biomedical knowledge in the management of the disorder.

To this end, a group of experts in genetics and clinical science coordinated by the National Center for Rare Diseases worked together with patient representatives to examine various aspects of appropriate treatment for ophthalmologic and oncologic problems in patients with congenital aniridia. Alongside clinical indications is a section on practical aids, organizational solutions, and reference professionals that can facilitate integration into the school system for children with congenital aniridia. Two other important areas the guidelines cover are care management and patient-care provider communication, its contents and means. The guidelines are addressed to healthcare professionals, healthcare and education policy decision makers, and regional agencies, with a view to provide them with a tool for clinical and organizational decision making.

Patients and their families will find the guidelines a helpful support for making active, informed choices in the management of the condition. Finally, the guidelines are intended to strengthen multidisciplinary collaboration between physicians, social workers, psychologists, educators, and other health and social care professionals in the provision of quality care through the services of the National Health System.

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Conflict of interest
The Authors declare that their professional judgement concerning the validation of the examined studies and the formulation of recommendations has not been influenced by secondary interests such as economic profit or personal interest.

Guide to the levels of evidence and strength of recommendations

The recommended guidelines are developed through the assessment of evidence and the strength of the recommendations themselves.

The evidence is assessed according to the quality and validity of relevant studies, their design and execution, and the probability that the knowledge provided by these studies is valid and exempt from systemic errors.

The strength of recommendations is based on the available evidence and its validity in application, thus representing the probability that these treatment and care recommendations will lead to improvements in the health of that section of the population for whom they have been developed.

Levels of evidence*

- **I** Evidences from randomized controlled clinical trials and/or systematic reviews of randomized trials
- **II** Evidences from one single adequately designed randomized trial
- **III** Evidences from non-randomized cohort studies with concurrent or historical control or their meta-analysis
- **IV** Evidences from non-controlled retrospective case- control studies
- **V** Evidences from non-controlled case-series studies
- **VI** Evidences from experts' opinions or opinions from panels as indicated in guidelines or consensus conferences, or based on opinions from members of the work group responsible for this guideline

Strenght of recommendations

- **A** Carrying out the specified procedure or diagnostic test is strongly recommended. The recommendation is supported by good-quality evidences, even if not necessarily type I or II
- **B** It would be inappropriate to always recommend the specified procedure or intervention, considered the still existing doubts, but it should anyway be carefully considered
- **C** Significant uncertainties exist against recommending to carry out the specified procedure or intervention
- **D** The specified procedure is not recommended
- **E** The specified procedure is strongly not recommended

* GCP Good Clinical Practice The procedure is recommended on the basis of the panel's opinion since evidence is not available

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Introduction

Epidemiology and clinical features of aniridia

Aniridia is an extremely rare eye condition. Its prevalence in Norway and Sweden is estimated to be 1:76,000 population and 1:70,000 population, respectively. [1] The estimated point prevalence is 1 in 40,000 live births in Denmark [2] and 0.42 in 100,000 live births in Spain. [3]

Aniridia (Online Mendelian Inheritance in Man [OMIM] 106210) is characterized by congenital hypoplasia of the iris which can vary considerably from milder forms to complete bilateral aplasia. It is associated with the early onset of nystagmus, photophobia, amblyopia, and severely decreased visual acuity. In adolescents and adults it can manifest itself with keratopathies, including central epithelial defects, corneal opacities, peripheral vascular pannus, and limbal stem cell deficiency. A further decrease in vision occurs with the development of cataracts, lens displacement and glaucoma. [4]

In 70% of cases, aniridia is inherited in an autosomal dominant fashion, while it is sporadic in about 30% of cases. [5] It is caused by mutations in the PAX6 gene (located on chromosome 11p), which plays an important role in cell differentiation and embryonic development, as it is involved in the morphogenesis of the eye, the olfactory bulb, the neural tube, the brain, and non-central nervous system organs such as the pancreas and the intestines. [2] In the majority of persons with aniridia, there is a loss of function of one copy of the gene PAX6: intragenic mutations are observed in two-thirds of cases, whereas chromosomal rearrangements are found in about one third (deletions, translocations, and inversions). The mutations can affect the structural gene or the regions of other genes that regulate development (e.g., SOX2), adhesion cells, and structural proteins of the cornea and lens.

Clinically, aniridia may manifest itself as an isolated eye abnormality without apparent systemic involvement or as part of a more complex constellation of conditions. Large alterations in chromosome 11p, comprising PAX6 and the adjacent WT1 gene, lead to a contiguous gene syndrome, the WAGR syndrome (Wilms tumor, Aniridia, Genitourinary abnormalities, and mental Retardation). [6]

The Gillespie syndrome (OMIM 206700), another extremely rare congenital condition, is characterized by aplasia of the pupil border, cerebellar ataxia, and delayed psychomotor development. Gillespie syndrome is genetically distinct from aniridia, although PAX6 mutations have been described in two persons with a phenotype similar to the Gillespie syndrome.

Genetic implications of aniridia

Giuseppe Damante, Angela Valentina D'Elia

The PAX6 gene

Aniridia is caused by mutations of the PAX6 gene that encodes a highly conserved transcription regulator involved in the ocular development of animals from the fruit fly (Drosophila melanogaster) to humans. [7-9] The PAX6 gene was cloned in 1991 [10] and in 1992 a cDNA homologue was isolated from mouse embryo. [11] The human and mouse proteins show nearly complete sequence homology and both proteins are members of the PAX protein family, comprising 9 members that share a paired domain. Each of the genes encoding PAX proteins has a tissue-specific expression; each PAX protein is involved in the development and function of one or more organs. The paired domain is about 120 amino acids long and is responsible for specific interactions with DNA sequences. The PAX6 protein interacts with the DNA sequences through the homeodomain which extends for about another 60 amino acids at the C terminal of the paired domain. [12]

The PAX6 gene is highly conserved phylogenetically. Nearly all animals have at least one gene very similar to human PAX6. For example, the fruit fly has a gene that encodes the paired domain and the homeodomain which has extended sequence homology with the human PAX6 gene; it is called eyeless (ey) because some of its mutant allelic variants are associated with ocular structure anomalies. [13]

In humans, the PAX6 gene is located on the short arm of chromosome 11 (11p13), about 22.4 kb long and comprising 14 exons. [9] The mature transcript of PAX6 is about 2.7 kb long. [10] PAX6 transcription is regulated by two promoters, P0 and P1, which are differently regulated by elements in cis and activated in tissue-specific fashion. [14,15]

The protein encoded by the PAX6 gene, in addition to the domains for interaction with DNA (paired and homeodomain), has a domain at the C terminal (PST), rich in proline, serine, and threonine. Preceding the PST region is a linker region, 78 amino acids long, which contains a high percentage of glycine (16.7%) and glutamine (12.8%) residues. [9]

The paired domain is subdivided into an N-terminal subdomain (residues 1-60) containing a beta short motif and three alpha-helices arranged in a helix-turn-helix motif, and a C-terminal subdomain (residues 77-133) containing three alpha-helices. There do not appear to be direct protein-protein interactions between the two subdomains.

The homeodomain is a protein domain with about 60 amino acids and is characterized by three alpha-helical-like structures (helix I, II and III) folded into a compact globular structure. [16,17]

The tissue-specific expression of the PAX6 gene is identical in the mouse and humans. It is expressed in various tissues during embryonic development and in the adult organism.

PAX6 plays a centrally important role in the complete development of the eye lens and the transcriptional activation of its structural genes, such as the zeta-crystallins. [18,19] It also plays a determinant role in the differentiation of pluripotent progenitors of the retinal cells and in maintaining their tissue-specific expression. [20,21] The presence of the isoform containing exon 5a ensures for correct eye growth. [21]

The PAX6 gene is expressed during the earliest stage of embryonic development of the pancreas and continues to be expressed in adult endocrine cells. Mutant mice homozygous for PAX6 lack cells able to produce pancreatic glucagon, suggesting that the gene is essential for the differentiation of pancreatic alpha cells. [22] In addition, PAX6, by binding to common elements in the promoters of genes for insulin, glucagon and somatostatin, activates the gene promoters that encode these hormones. [23] Reports have described cases of patients presenting aniridia and diabetes associated with PAX6 mutations, suggesting that the two conditions share a common

regulating mechanism. [24]

In the nervous system, PAX6 controls the migration and differentiation of several specific progenitors of neural brain cells. The presence of PAX6 in association with Emx2 factor regulates the formation of cortical areas and confers area identity to diverse cells. [25,26] Analysis of its genetic expression in mutant mice has shown that PAX6 regulates the expression of Neurog2 in the spinal cord and differentially controls distinct enhancers along the dorsoventral axis. [27] Radial glial cells, precursors of astrocytes, are ubiquitous in the central nervous system during its development. Experimental studies have shown that cells isolated from the cortex of mice mutant for PAX6, have less neurogenic potential, suggesting the importance of PAX6 in the differentiation of the central nervous system. [28]

PAX6 is also involved in the development of Rathke's pouch and the anterior pituitary gland; its expression is essential for the differentiation of various types of cells (somatotropic, lactotropic, thyrotropic) along the dorsoventral axis of the adenohypophysis. [29]

A study on the molecular basis for hypophyseal dysfunctions in the mouse and humans identified 12 transcription factors considered critical for hypophyseal development and function, including the PAX6 gene. [30]

Genetic basis of aniridia

Aniridia is transmitted in autosomal dominant fashion. Each gene in every cell is present in two copies (alleles) one each from both parents. A disorder is referred to as dominant when it is expressed in a heterozygous person (i.e., a person with only one mutant allele). The affected person transmits the mutation on average to 50% of his or her children, irrespective of the sex of the child. Most persons with aniridia (about 70%) have a parent with the condition (familial aniridia), whereas the remaining 30% do not (sporadic aniridia). [31] Sporadic aniridia arises from a new mutation during gametogenesis. The rate of pathogenetic mutation of the PAX6 gene is about 10^{-5} to 10^{-6}, meaning that each healthy individual has a probability between 1:100,000 and 1:1,000,000 of having a child with aniridia caused by a new mutation.

Aniridia may manifest itself clinically as an isolated ocular anomaly caused by point mutations in PAX6 or by deletions of the structural gene or the regions regulating its expression. In 15% of cases, aniridia is the clinical expression of the WAGR syndrome (Wilms tumor, a rare kidney cancer; Aniridia; Genitourinary abnormalities; and mental Retardation) which is caused by a cytogenetically visible deletion in the 11p13 band or by a submicroscopic deletion involving the PAX6 gene and the adjacent WT1 gene. [32]

An interactive database for the analysis of PAX6 mutations is available at http://lsdb.hgu.mrc.ac.uk/home.php?select_db=PAX6. The database currently contains information on 309 mutations, 286 of which are associated with congenital eye defects and 23 apparently neutral polymorphisms. [33, 34] The pathogenic mutations comprise: 102 nonsense mutations (35.7% of the total); 68 frameshift deletions or insertions (23.8%); 50 missense mutations (17.5%); 36 splicing mutations (12.6%); 16 in frame deletions or insertions (5.6%); and 14 run on mutations (4.8%). Nonsense mutations introduce a premature stop codon; in splicing mutations and frameshift deletions or insertions, the protein following the mutation is strongly altered and therefore nonfunctional. These three categories of mutations constitute over 72% of all pathogenic mutations identified to date. [32-36] Of the 286 pathogenic mutations present in the database, 257 (89.9%) are associated with aniridia and 29 (10.1%) with other phenotypes such as a foveal hypoplasia, microophthalmia, and optic nerve defects. [33, 34] Among the mutations responsible for aniridia, few missense (1.7%) mutations encode proteins with a likely loss of function. [34,37-40] Of the 29 mutations known to be associated with eye defects (without aniridia), 69% are missense mutations. [34]

This means that aniridia is more often associated with mutations that lead to complete inactivation of the protein (nonsense mutations, frameshift, splicing, deletion of the entire gene or a significant part of it), whereas other ocular phenotypes are associated with missense mutations. This is probably because missense mutations lead to changes in a single amino acid. This class of mutations does not completely inactivate protein function but rather modifies it, resulting in a phenotype different from aniridia.

Missense mutations are generally located in the paired domain (exons 5, 5a, 6, and 7) and are associated with phenotypes that affect the tissues involved in aniridia, such as the fovea, the optic nerve, and the iris. [41,42]

The mutations that introduce a premature stop codon have presumably a negative dominant effect in that the PAX6 protein trunk containing only the domains for DNA binding could acquire a major capacity for binding the target sequences without activating the genes downstream and thus interfere with normal protein function. [43,44]

It could be expected that the mutations that truncate the normal protein sequence of PAX6 are associated with a less severe form of the condition (or do not lead to its development) if the mutation alters only the C-terminal of the proteins while sparing the functional domains. Actually, however, genotype-phenotype correlations of mutations in the database suggest that the position of the truncating mutation does not have a precise role, hence the phenotype consequences in vivo. The truncating mutations associated with aniridia are not correlated with their location. [34] It is possible that nonsense-mediated decay is the pathogenically responsible molecular mechanism. Nonsense-mediated decay is the mechanism through which mRNAs containing a premature stop codon are decayed before they can produce large amounts of protein trunks. [45] The available data suggest the hypothesis that aniridia is due to haploinsufficiency because of the loss of allele function. This does not appear to be due to premature termination of the protein but rather to the nonsense-mediated delay mechanism. [33,34]

The majority of patients (80-90%) with aniridia are heterozygous for PAX6 mutations[46] (see also the database mentioned above). In humans, homozygous mutations (i.e., when both alleles carry the mutation) are lethal and cause a phenotype similar to that seen in the mouse, characterized by anophthalmia and central nervous system defects. [47] Also other organisms with homozygous PAX6 mutations present anomalous phenotypes, for example, small eye mice, eyeless Drosophila, and Caenorhabditis elegans. [13,48-50] Homozygous small eye mice die shortly after birth, have no eyes or nasal cavities and present brain defects. [7]

Genetic analysis

Point mutations of the PAX6 gene are identified by DNA sequencing. The deletions (small and large) are identified with molecular (multiple ligation-dependent probe amplification [MLPA]) or cytogenetic techniques (fluorescent in situ hybridization [FISH]). In these cases the possible deletion of the WT1 gene, associated with the risk of Wilms tumor in the WAGR syndrome, is evaluated.

The sensitivity of genetic testing (i.e., a test's ability to identify a mutation) is less than 100%. In the WAGR syndrome, cytogenetic screening has a sensitivity of about 70%. In isolated aniridia, the complete panel of molecular tests has a sensitivity of about 65%.

When a pathogenic mutation is detected in a person with aniridia, screening can be extended to other family members. Pregnant women may be offered prenatal genetic testing (chorionic villous sampling CVS or amniocentesis).

Theoretically, preconceptional genetic testing is another possibility, analyzing the first polar globule of an affected mother.

In cases of de novo mutation, the neonate should be tested for the possible involvement of the WT1 gene, due to the higher risk of developing Wilms tumor.

Genetic analysis of PAX6 is indicated when isolated or syndromic aniridia (WAGR) is present, as well as other disorders potentially associated with PAX6 mutations (Peters anomaly, papillary ectopia, foveal hypoplasia, coloboma, optic nerve hypoplasia).

Medically, genetic testing is useful for differentiating aniridia caused by mutations only in the PAX6 gene from those forms associated with the deletion of contiguous genes.

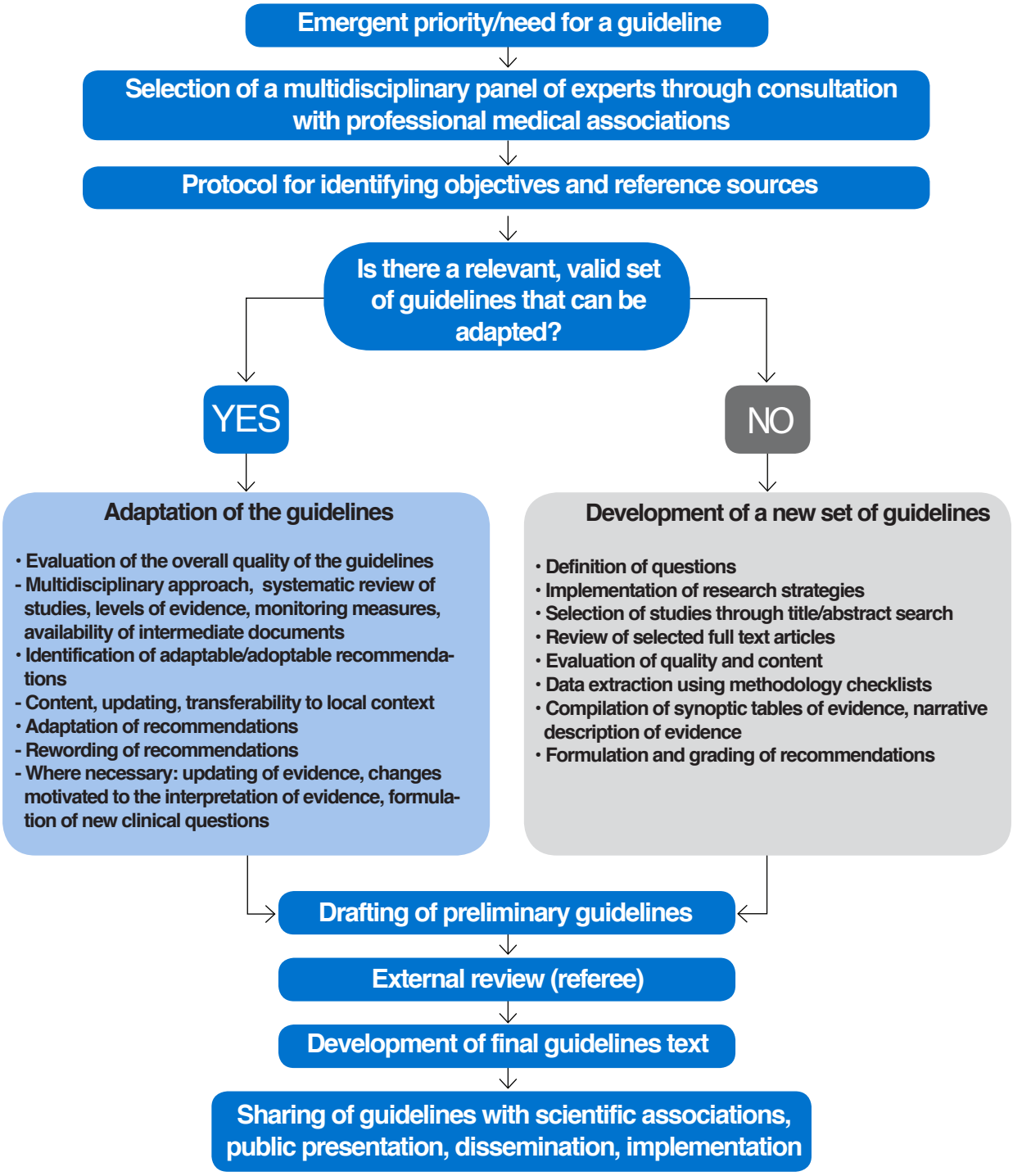
References

1. Edén U, Iggman D et al. Epidemiology of aniridia in Sweden and Norway. Acta Ophthalmol 2008;86:727-9.
2. Grindley JC, Davidson DR, Hill RE. The role of Pax-6 in eye and nasal development. Development 1995;121:1433-42.
3. Bermejo E, Martínez-Frías ML. Defectos congénitos oculares:algunos aspectos clínicos y epidemiológicos. Bol ECEMC: Rev Dismor Epidemiol 2002;1:43-8.
4. Tornqvist K. Aniridia: sight-threatening and hard to cure. Acta Ophthalmol 2008;86:704-5.
5. Valenzuela A, Cline RA. Ocular and nonocular findings in patients with aniridia. Can J Ophthalmol 2004;39:632-8.
6. Crolla JA, van Heyningen V. Frequent chromosome aberrations revealed by molecular cytogenetic studies in patients with aniridia. Am J Hum Genet 2002;71:1138-49.
7. Hill RE, Favor J et al. Mouse Small eye results from mutation in a paired-like omeobox containing gene. Nature 1991;354:522-5.
8. Jordan T, Hanson I et al. (1992) The human PAX6 gene is mutated in two patients with Aniridia.Nature Genet 1992;90:41-54.
9. Glaser T, Walton DS, Maas RL. Genomic structure, evolutionary conservation and Aniridia mutations in the human PAX6 gene. Nature Genet 1992;2:232-8.
10. Ton CC, Hirvonen H et al. Positional cloning and characterization of a paired box - and homeobox - containing gene from the Aniridia region. Cell 1991;67(6):1059-74.
11. Ton CC, Miwa H, Saunders GF. Small eye (Sey): cloning and characterization of the murine homolog of the human Aniridia gene. Genomics 1992;13(2):251-6.
12. Stuart ET, Kioussi C, Gruss P. Mammalian Pax genes. Annu Rev Genet 1993;27:219-36.
13. Quiring R, Walldorf U et al. Homology of the eyeless gene of Drosophila to the Small eye gene in mice and Aniridia in humans. Science 1994;265:785-9.
14. Plaza S, Dozier C et al. Quail Pax-6 (Pax-QNR) mRNAs are expressed from two promoters used differentially during retina development and neuronal differentiation. Mol Cell Biol 1995;15:3344-53.
15. Plaza S, Saule S, Dozier C. High conservation of cis-regulatory elements between quail and human for the Pax-6 gene. Dev Genes Evol 1999;209:165-73.
16. Tsao DH, Gruschus JM et al. The three dimensional solution structure of the NK-2 homeodomain from the Drosophila. J Mol Biol 1995;251:297-307.
17. Esposito G, Fogolari F et al. Analysis of the solution structure of the homeodomain of rat thyroid transcription factor 1 by 1H-NMR spectroscopy and restrained molecular mechanics. Eur J Biochem 1996;241:101-13.
18. Ashery-Padan R, Marquardt T et al. Pax6 activity in the lens primordium is required for lens formation and for correct placement of a single retina in the eye. Genes Dev 2000;14:2701-11.
19. Richardson J, Cvekl A, Wistow G. Pax-6 is essential for lens-specific expression of z-crystallin. Proc Natl Acad Sci USA 1995;92:4676-80.
20. Marquardt T, Ashery-Padan R et al. Pax6 is required for the multipotent state of retinal progenitor cells. Cell 2001;105:43-55.
21. Mann RS. Two Pax are better than one. Nature Genet 2004;36:10-1.
22. St-Onge L, Sosa-Pineda B et al. Pax6 is required for differentiation of glucagon-producing alpha-cells in mouse pancreas. Nature 1997;387:406-9.
23. Sander M, Neubuser A et al. Genetic analysis reveals that PAX6 is required for normal transcription of pancreatic hormone genes and islet development. Genes Dev 1997;11:1662-73.
24. Yasuda T, Kajimoto Y et al. PAX6 mutation as a genetic factor common to Aniridia and glucose intolerance. Diabetes 2002; 51:224-30.
25. Glaser T, Jepeal L et al. PAX6 gene dosage effect in a family with congenital cataracts, Aniridia, anophthalmia and central nervous system defects. Nature Genet 1994; 7:463-71.
26. Bishop KM, Goudreau G, O' Leary DD. Regulation of area identity in the mammalian neocortex by Emx2 and Pax6. Science 2000;288:344-9.
27. Scardigli R, Schuurmans C et al. Crossregulation between neurogenin2 and pathways specifying neuronal identity in the spinal cord.

Neuron 2001;31:203-17.
28. Heins N, Malatesta P et al. Glial cells generate neurons: the role of the transcription factor Pax6. Nature Neurosci 2002;5:308-15.
29. Kioussi C, O'Connell S et al. Pax6 is essential for establishing ventral-dorsal cell boundaries in pituitary gland development. Proc Nat Acad Sci 1999;96:14378-82.
30. Cushman LJ, Camper SA. Molecular basis of pituitary dysfunction in mouse and human. Mammalian Genome 2001;12:485-94.
31. Valenzuela A, Cline RA. Ocular and nonocular findings in patients with Aniridia. Can J Ophthalmol 2004;39:632-8.
32. Crolla JA, Van Heyningen V. Frequent chromosome aberrations revealed by molecular cytogenetic studies in patients with Aniridia. Am J Hum Genet 2002;71:1138-49.
33. Prosser J, van Heyningen V. PAX6 Mutation Reviewed. Human Mutation 1998; 11:93-108.
34. Tzoulaki I, White IM, Hanson IM. PAX6 mutations: genotype-phenotype correlations. BMC Genetics 2005;6:27-39.
35. Fisher E, Scambler P. Human haploinsufficiency – one for sorrow, two for joy. Nat Genet 1994;7:5-7.
36. Fantes J, Redeker B et al. Aniridia-associated cytogenetic rearrangements suggest that a position effect may cause the mutant phenotype. Hum Mol Genet 1995;4:415-22.
37. Tang HK, Chao LY, Saunders GF. Functional analysis of paired box missense mutations in the PAX6 gene. Hum Mol Genet 1997;6:381-6.
38. Azuma N, Hotta Y et al. Missense mutations in the PAX6 gene in Aniridia. Invest Ophthalmol Vis Sci 1998;39:2524-8.
39. Vincent MC, Pujo AL et al. Screening for PAX6 gene mutations is consistent with haploinsufficiency as the main mechanism leading to various ocular defects. Eur J Hum Genet 2003;11:163-9.
40. Chauhan BK, Yang Y et al. Functional interactions between alternatively spliced forms of Pax6 in crystallin gene regulation and in haploinsufficiency. Nucleic Acid Res 2004; 32(5):1696-709.
41. Azuma N, Yamaguchi Y et al. Mutations of the PAX6 gene detected in patients with a variety of optic-nerve malformations. Am J Hum Genet 2003;72:1565-70.
42. Hanson I, Churchill A et al. Missense mutations in the most ancient residues of the PAX6 paired domain underlie a spectrum of human congenital eye malformations. Hum Mol Genet 1999;8:165-72.
43. Singh S, Tang HK et al. Truncation mutations in the transactivating region of PAX6 result in dominant-negative mutants. J Biol Chem 1998;273(34):21531-41.
44. Duncan MK, Cvekl A et al. Truncated forms of Pax6 disrupt lens morphology in transgenic mice. Invest Ophthalmol Vis Sci 2000;41:464-73.
45. Byers PH. Killing the messenger: new insights into nonsense-mediated mRNA decay. J Clin Invest 2002;109:3-6.
46. van Heyningen V, Williamson KA. PAX6 in sensory development. Hum Mol Genetics 2002;11(10):1161-7.
47. Hodgson SV, Saunders KE. A probable case of the homozygous condition of the Aniridia gene. J Med Genet 1980;17:478-80.
48. Matsuo T, Osumi-Yamashita N et al. A mutation in the Pax-6 gene in rat small eye is associated with impaired migration of midbrain crest cells. Nature Genet 1993;3:299-304.
49. Chisholm AD, Horvitz HR. Patterning of the Caenorhabditis elegans head region by the Pax-6 family member vab-3. Nature 1995;377:52-5.
50. Zhang Y, Emmons SW. Specification of senseorgan identity by Caenorhabditis elegans Pax-6 homologue. Nature 1995;377:55-9.

Methods

Guideline preparation and development



Aim and targets

The main objective of this guideline is to define recommendations for the management of ophthalmologic, rehabilitation and social problems related to aniridia. The guideline is addressed to ophthalmologists, primary care physicians, pediatricians, neonatologists, gynecologists, pediatric oncologists, infantile neuropsychiatrists, psychologists, physiotherapists/psychomotor specialists, orthoptists, clinical pedagogy specialists, social workers, educators for the blind and visually impaired, patients and their families, educators, and health care policy makers.

Limitations

The guideline has the following limitations:

- The molecular genetic diagnosis and differential diagnosis of aniridia are not discussed.
- A cost-efficacy analysis of intraocular lens implantation was not performed (IOL, Intra Ocular Lens and IOL-BDI, Intra Ocular Lens - Black Iris Diaphragm).

Guideline committee

Diverse work groups collaborated on drawing up the guideline:

- The multidisciplinary panel formulated the questions, selected the studies included in the guide line, redacted the summary, and formulated the recommendations.
- The information specialist from the Istituto Superiore di Sanità designed the search strategies and searched the bibliographic databases.
- The coordinators supervised the organization, management of the work groups, programming and supervision of activities.
- The editorial coordinator and redactors reviewed the tests and managed communications between the panel members and the editorial office.
- The technical-administrative secretarial office set up the web community for the guideline work groups, retrieved the scientific articles, and handled the administrative relations with the editorial office.
- The reviewers evaluated the document.

Guideline development process

Selection of topic and identification of objectives

Clinical practice guidelines can be created for any topic or health care procedure. However, because this process requires resources, most national and international organizations that generate guidelines and other documents (health technology assessments and systematic literature reviews) necessarily operate choices according to explicit criteria and procedures. [1]

The National Center for Rare Diseases of the Istituto Superiore di Sanità ([Centro nazionale malattie rare] CNMR-ISS) prefers as a selection criterion, together with the epidemiological criterion of the rarity of a disease, that of demand in response to the needs of health care providers and patient associations. The Center's objective in publishing and disseminating the guideline is to reduce uncertainty and variability in clinical decision making and ultimately to improve the care and the quality of life of patients.

With regard to this guideline, a group of promoters composed of clinical experts and representatives of the Italian Aniridia Association requested that the Center draw up a document that dealt specifically with the management of congenital aniridia, with a view to facilitate the transfer of knowledge from biomedical research into clinical practice and to improve social and health care and the quality of life of patients and their families.

The project, within which the need for creating the guideline was defined, was funded within the framework of the "Rare Diseases: From Surveillance to Information" program of the Ministry of Health.

Selection of the multidisciplinary panel

The panel was formed by experts in the diagnosis and treatment of aniridia and related condi-

tions: geneticists, ophthalmologists, and pediatric oncologists. The panel also included patient representatives.
The panel members compiled and submitted a conflict of interest disclosure statement and a statement of approval of the final document.
After the first meeting, the work group communicated principally via email or telephone. A web community was set up on the Center web site to collect the bibliographic material.

Bibliographic research
The bibliographic research was carried out through search strategies especially designed by the information specialist of the documentation sector of the Istituto Superiore di Sanità. The search was performed by searching the Medline and Embase databases for articles published between 1988 and February 2011, without language restrictions. In addition to the studies retrieved from the search, other reference material the experts deemed useful for systematically developing the recommendations was also included.

Formulation of recommendations
The expert panel selected and summarized the evidence, from which the recommendations were formulated and graded. The grading method is described in the methodology manual of the National Guidelines Program [2] which foresees six levels of evidence (I-VI) and five grades of strength of recommendations (A-E). The grading scheme is illustrated on page 5. For the questions for which no specific studies were available, the recommendations were formulated on the basis of panel opinions and are marked GCP (good clinical practice).
The experts shared the recommendations reported in the guidelines. Reservation was expressed by Dr. Rama in relation to recommendations regarding Questions 8A, 11A, and 11B.

External review of the final document
The document shared by the panel was sent to external experts to obtain their opinion of the readability and clarity of the document and the coherence between the summaries of the evidence and the derived recommendations, to examine the completeness of the bibliographic sources, and to express their professional opinions where no evidence was provided.
The reviewer group included experts in genetics, pediatric oncology and eye specialists.

Updating and implementation
An update of the guideline is planned within 3 years after the publication of this document. The intervention strategies for the dissemination of the document and efficacious implementation are:
- Presentation at national and international conferences
- Publication on Internet sites: National Guidelines System (Sistema nazionale linee guida [SNLG]), CNMR, scientific societies
- Promotion of formal adoption by local health boards, hospitals, medical specialists, primary care physicians, and pediatricians
- Promotional campaigns targeting scientific societies and research groups.

Availability of the full text
The full text of the guideline is available at the web site of the National Center for Rare Diseases, http://www.iss.it/cnmr and the National Guidelines System http://www.snlg-iss.it/lgmr_aniridia_congenita.

References

1. Oxman AD, Schünemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. Health Res Policy Syst 2006;4:14.
2. Programma nazionale per le linee guida – Istituto superiore di sanità. Manuale metodologico. Come produrre, diffondere e aggiornare raccomandazioni per la pratica clinica. PNLG, Roma, 2002. Disponibile all'indirizzo: http://www.snlg-iss.it/manuale_metodologico_SNLG (consulted 10-12-2012).

Genetic counseling

Giuseppe Damante, Angela Valentina D'Elia

Questions and recommendations

Question 1. Why is genetic counseling advised for patients with aniridia?

Genetic counseling is a process of communication between genetics professionals and patients or their families who are (or believe they are) at risk of developing an inheritable genetic disorder, and are concerned about the medical and genetic health, the diagnosis, the prognosis, the therapy and the risk of occurrence in other family members.
The Italian Society of Human Genetics and the European Commission recommend that genetic testing be accompanied by genetic counseling (before and after testing) in order to understand the implications of the test results, the advantages and limitations of testing, and to decide whether it is advisable.
Also in patients with aniridia genetic counseling before and after testing is both necessary and useful for obtaining detailed information on test results, the implications for the risk of recurrence of the disorder, the utility of extending testing to other family members, and to discuss whether screening for future at-risk pregnancy should be performed.

Recommendations

GCP Following clinical diagnosis of aniridia, individuals affected with the disorder and their family members should be offered genetic counseling to discuss the characteristics of the disorder, the model of genetic transmission, and the risk of recurrence. Available genetic tests should be illustrated to support the clinical diagnosis and to monitor for future at-risk pregnancy.

GCP Genetic counseling will evaluate whether the form of the disorder is sporadic or familial. This aspect has important consequences on estimating the risk of recurrence in other family members of the individual(s) affected. Assessment of risk recurrence in family members and discussion of possible options to mitigate such risk (e.g., prenatal genetic testing) are fundamental steps in genetic counseling. Genetic testing should be performed only after genetic counseling.

GCP During a genetic counseling session the advantages and limitations of genetic tests should be made clear. There are basically two advantages: knowledge of the mutation causing the disorder in a family will permit potential prenatal diagnosis; knowing that the causal mutation may be a deletion including the WT1 gene will aid in assessing the risk of developing Wilms tumor. Genetic testing should provide for the possibility to identify the point mutation (by gene sequencing) and large deletions of the gene (by fluorescent in situ hybridization [FISH] or multiplex ligation-dependent probe amplification [MLPA]).

GCP The major limitation of genetic testing is that the causal mutation may be identified in only 50-60% of cases. During genetic counseling it is necessary to clarify that a negative test result does not necessarily mean the absence of mutation but rather that the mutation could not be detected. Only in familial cases, when the test is negative for detecting the mutation of the PAX6 gene, can the possibility of transmission of a genomic fragment containing the mutation (and therefore the possibility of prenatal diagnosis) be performed by an indirect approach to diagnosis through linkage.

GCP Patients and their family members should demonstrate that they have understood the information received during a genetic counseling session.

Aniridia and the ocular surface

Paolo Rama, Maurizia Viganò

The ocular surface

The ocular surface is now considered as an integrated functional unit comprising the conjunctiva, the limbus, the cornea, and the locoregional lubrication, nervous and immune systems. [1] All system components work together to maintain the equilibrium needed for keeping the cornea transparent.

The conjunctiva is a mucous membrane that lines the internal surface of the eyelids and extends on the surface of the globe to the limbus. Its main functions are to produce the mucosal layer of tear film and to protect the eye through immune tissue and agents with antibacterial and antiviral activity. [2]

The sclerocorneal limbus constitutes the transition area between the cornea and the conjunctiva. Clinical and experimental studies suggest that the basal cells of the limbal epithelium are the stem cells of the corneal epithelium. [3-5] Common to all stem cells is their capability for asymmetric division: one daughter cell remains a stem cell while the other differentiates. These daughter cells, termed transient amplifying cells, have a high proliferative capability that provides the high number of epithelial cells needed for renewal of the corneal epithelium or to repair the loss of cells following trauma. [6-9]

The cornea consists of a transparent, avascular layer in continuity with the sclera. It is composed of five layers, from outermost to the inner layer: epithelium, Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. The cornea works mainly as a positive lens that, together with the lens, converges the light rays, focusing them on the retina. This is possible thanks to its transparency and resistance.

The tear film is a complex system that comprises mucin, glycoproteins, lipids, lipoproteins, and glycolipids. It helps to protect and nourish the ocular surface and maintain corneal transparency. [10]

The cornea is the body's most enervated tissue. The nerve endings are composed of sensitive myelinic fibers coming from the first branch of the trigeminal nerve. The nerve endings constitute a dense network of nociceptors, which explains the cornea's sensitivity to external stimuli. The corneal sensory nerves constitute the afferent branch of two reflex arches that cause lacrimation and blinking. The trigeminal nerve fibers also exert trophism on the corneal epithelium, stimulating mitosis and promoting repair processes. [11]

Alterations of the ocular surface in aniridia

Unlike other congenital anomalies such as the lack of the iris or cataracts, alterations of the corneal surface manifest themselves with time. The conjunctiva is not usually affected in aniridia. [9,11-17]

Cornea and limbus

Normally transparent at birth, the cornea begins to gradually lose its transparency over time due to the formation of a superficial neovascularized pannus, with onset usually around 18 to 20 years of age. Several studies [17,18] have hypothesized that the invasion by neovascularized tissue results from a deficit in limbal stem cells. It is not clear whether this process is due to a congenital abnormality in limbal stem cells or their depletion or altered regulation. An understanding of these mechanisms will be fundamental for developing new treatment strategies.

Limbal deficit manifests itself initially with epithelial problems: recurrent erosion, persistent ulceration, opacity and epithelial fibrosis, ensuing in reduced vision, pain, and photophobia. [19,20]
With time, owing to the absence of the corneal epithelium, the corneal surface becomes covered by a vascularized conjunctival epithelium, so-called corneal conjunctivalization. [13] The conjunctival epithelium creates a state of chronic, initially mild, inflammation the patient perceives as a foreign-body sensation, burning and photophobia. With time, the conjuctival epithelium can cover the cornea completely, resulting in a marked decrease in vision.
Persistent inflammation leads to the formation of whitish-gray nodular lesions initially localized to the peripheral ring and then progressing to the central area, as occurs in Salzmann's nodular degeneration. [21]
As the condition evolves, the corneal pannus enlarges, leading to scaring of the central stroma and neovascularization. [22,23]
A typical structural element of the cornea in patients with aniridia is the increase in corneal thickness before the onset of edema. Several studies have reported a mean corneal thickness of 631 microns in 32 eyes in 17 patients, 100 microns greater than the average normal corneal thickness. [21,24]

Questions and recommendations

Question 2 Which tests are performed in the diagnosis of stem cell deficit of the corneal epithelium (so-called limbal deficit)?

Limbal stem cell deficit manifests itself with characteristic clinical signs: in the early stages persistent or recurrent epithelial deficits, pain and photophobia are present; in advanced stages, there may be corneal ulcerations and a vascularized pannus that stabilizes the condition, eliminating the epithelial defects but seriously reducing vision.
Examination with fluorescein staining distinguishes the corneal epithelium, which is impermeable to the dye, from the conjunctival epithelium which is more permeable to the dye. The epithelium can also be examined by taking a superficial biopsy for impression cytology, which more accurately distinguishes corneal from conjunctival epithelium. [16] This exam is easy and quick to perform and permits the study of the epithelia with the use of specific dyes. [25-28] However, because of its invasiveness, it creates a defect at the biopsy site which may be painful and require several weeks to heal in diseased eyes such as in the setting of aniridia. Therefore, it should be reserved for selected patients and in response to specific questions.
Recently, confocal microscopy has been employed in the diagnosis of limbal deficit. It is less invasive than impression cytology and may in future allow the quantification of limbal damage, follow progression of the disease, and evaluate the outcome after medical or surgical treatment. [21,29-31]
The tear film may be altered in aniridia. While aqueous secretion does not appear to be impaired, changes in the mucosal component have occasionally been found. Two studies [12,32] suggested that dry eye is caused by a deficit in the mucosal component and found a reduction in the number of conjunctival goblet cells, whereas other studies reported an increase in number. Lipid evaluation has produced contradictory results: one study [32] reported mild blepharitis of no clinical relevance, whereas the other [12] described stenosis and atrophy of the fornices of the meibomian glands in 77.8% of patients.
It has also been hypothesized that epithelial dystrophy, secondary to limbal deficit, can alter tear film adhesion to the corneal surface, creating a condition similar to dry eye. [12,32]

Recommendations

VI/A In the diagnosis of corneal manifestations, clinical assessment followed by slit-lamp examination should be performed.

VI/A If the cornea is opaque, optical coherence tomography (OCT) may be helpful for more precisely establishing the depth of the opacity and to examine the structures of the anterior segment if they cannot be visualized due to severe loss of corneal transparency.

VI/A For the diagnosis of limbal deficit, clinical assessment in conjunction with slit-lamp examination is recommended.

VI/B Impression cytology is more comprehensive than slit-lamp examination since it permits accurate assessment of corneal damage. However, owing to its invasiveness associated with serious epithelial defects, its utility should be considered on a case-by-case basis.

VI/A Confocal microscopy is less invasive than impression cytology and may in future allow assessment of limbal damage, monitor progression of the disease, and evaluate outcome after medical or surgical treatment.

VI/A In the diagnosis of altered tear film the Schirmer test is indicated in conjunction with the break-up time test (BUT) and observation of the ocular surface with slit-lamp examination after instillation of vital dyes such as fluorescein, rose bengal or lissamine green.

Question 3. How effective are available treatments for the manifestations of aniridia on the ocular surface?

Currently, the objective of treatment is to manage the manifestations of the disease. Dry eye is treated with artificial tears administered as eye drops or gel, preferably using preservative-free products. An ointment may be applied before going to bed to obtain prolonged effect. The use of 50% autologous serum eye drops has also been suggested. [14,33] The serum is a tear substitute much more similar to natural tears than is a lubricating gel; however it is difficult to prepare and is associated with the risk of contamination and infections. Therefore, it is advised only in selected cases when artificial tears are ineffective. Lastly, scleral contact lenses may offer the advantage that they maintain moisture between the lens and the ocular surface.

In recurrent epithelial defects, the preferred choice of treatment is to increase the frequency of application of preservative-free lubricant eye drops. Therapeutic soft contact lenses may be worn to relieve pain symptoms and to protect the corneal surface, and promote re-epithelialization. There is no evidence that eye bandaging promotes re-epithelialization; therefore, the choice of whether or not to bandage is up to the patient. In such cases, the use of autologous serum eye drops may be useful. In recalcitrant cases, amniotic membrane grafting has been demonstrated highly efficacious in relieving pain symptoms and promoting rapid re-epithelialization. The amniotic membrane is immunologically inert, possesses anti-inflammatory, bacteriostatic, and antiangiogenic properties and it can stimulate the growth of stem cells. [34,35]

In the loss of corneal transparency due to vascularization and stromal opacity, corneal transplant, either lamellar or perforating, is unlikely to be successful because the grafted corneal epithelium has to be gradually substituted by the epithelium of the recipient cornea. If the limbus

of the recipient cornea is altered, it will not be able to produce transparent corneal epithelium; instead, a conjunctival epithelium will again migrate, forming a vascularized pannus also on the transplanted cornea. For these reasons, corneal transplants are no longer offered except in particular cases. [36]

To repopulate the limbus with stem cells, grafting with limbal stem cells harvested from a living or dead consanguineous donor has been proposed. Despite the encouraging initial results, in the long term a vascularized pannus recurs with signs of depletion of the grafted stem cells due to graft rejection. [18,37,38] This observation has been confirmed by studies that showed that following grafting of allogenic limbal stem cells the donor's epithelial cells could not be isolated from the recipient several years after the intervention. [39,40]

Recently, grafting of autologous stem cells (i.e., the patient's own cells) from the oral epithelium has been attempted[15]; however, it is still too early to say whether this method can stably restore the corneal epithelium and its transparency.

Much hope has been placed on the possibility to construct a synthetic analogue of corneal tissue (so-called artificial cornea); however, no true substitute for the cornea has been found to date. Today, the only alternative to corneal transplants in severe cases, such as those caused by bilateral total limbal deficit or absence of tears, is osteodontokeratoprosthesis. This procedure, first conceived of in the 1960s, utilizes a dental lamina to create an alternative biological support to the cornea with less risk of extrusion as compared to synthetic prosthetic grafts. [41-43] Other types of keratoprosthesis, for example, Boston keratoprosthesis, can give good short-term results but are associated with long-term problems and should therefore be considered with caution. [44-49]

Recommendations

VI/A In cases of dry eye, the use of artificial tears as eye drops or gel, preferably preservative-free products, is recommended.

VI/B An ointment may be applied before bedtime to obtain a prolonged effect.

V/B In more severe cases, the use of autologous serum eye drops may be helpful. Cases should be selected according to real need owing to the potential risk of eye drop contamination and infections. The risk can be minimized with the use of single-use products. It is hoped that blood banks, responsible for the treatment of blood derivates, will eventually provide this service.

VI/B Scleral contact lenses offer the advantage that they protect the ocular surface by maintaining moisture between the lens and the ocular surface.

VI/B In case of epithelial defects, the frequency of instillation of preservative-free lubricants should be increased and an ointment applied at bedtime. Therapeutic soft contact lenses may be used to relieve pain, protect the corneal surface, and promote re-epithelialization. There is no evidence that bandaging can promote re-epithelialization; therefore, the patient should decide whether he or she feels bandaging brings benefit.

VI/A In persistent epithelial defects, a therapeutic soft contact lens should be continuously worn until re-epithelialization is complete, substituting it every 2-3 weeks. In recalcitrant cases, amniotic membrane grafting has been shown highly efficacious in relieving pain and promoting rapid re-epithelialization.

In cases of loss of corneal transparency associated with the formation of vascularized corneal pannus (sign of limbal deficit):

VI/A Lamellar or perforating corneal transplant is not recommended.

V/A Donor limbal stem cell grafts are of limited duration.

V/B The results of studies on stem cells harvested from other sites in the patient (e.g., the oral mucosa) are so far inconclusive.

V/B The outcome after osteodontokeratoprosthesis is more stable but the procedure is complex.

V/B Other types of keratoprosthesis, e.g., Boston type, may produce good short-term benefit but can create problems with time and should therefore be considered with caution.

VI/B In case of loss of transparency without corneal pannus formation, corneal transplant, preferably lamellar, may be considered.

References

1.Tsubota K, Tseng SCG, Nordlund ML. Anatomy and physiology of the ocular surface. In: Holland EJ (ed). Ocular surface disease: medical and surgical management. Springer-Verlag, New York, 2002.

2. Gipson IL. Anatomy of the conjunctiva, cornea and limbus. In: Smolin G, Thoft RA (ed). The cornea (III ed). Little, Brown and Company publisher, Boston, 1994 (pp.3-22).

3. Schermer A, Galvin S, Sun TT. Differentiationrelated expression of a major corneal keratin in vivo and in culture suggests limbal location of corneal epithelial stem cells. J Cell Biol 1986;103:49–62.

4. Cotsarelis G, Cheng SZ et al. Existence of slowcycling limbal epithelial basal cells that can be preferentially stimulated to proliferate: implications on epithelial stem cells. Cell 1989;57:201-9.

5. Pellegrini G, Golisano O et al. Location and clonal analysis of stem cells and their differentiated progeny in the human ocular surface. J Cell Biol 1999;145(4):769-82.

6. Barrandon Y. The epidermal stem cell: an overview. Dev Biol 1993;4:209-15.

7. Lavker RM, Miller S et al. Hair follicle stem cells: their location, role in hair cycle, and involvement in skin tumor formation. J Invest Dermatol 1993;101(Suppl):16S-26S.

8. Morrison SJ, Shah NM, Anderson DJ. Regulatory mechanisms in stem cell biology. Cell 1997;88:287-98.

9. Miller SJ, Lavker RM, Sun TT. Keratinocyte stem cells of cornea, skin, and hair follicle. In: Potten C (ed). Stem Cells. Academic Press, New York, 1997 (pp. 331-62).

10. Rieger G. The importance of the precorneal tear film for the quality of optical imaging. Br J Ophthalmology 1992;76:157-8.

11. Muller LJ, Marfurt CF et al. [Erratum to: Muller LJ, Marfurt CF et al. Corneal nerves: structure, contents and function. Exp Eye Res 2003;76:521-42]. Exp Eye Res 2003;77:253.

12. Jastaneiah S, Al Rajhi AA. Association of Aniridia and dry eyes. Ophthalmology 2005;112:1535-40.

13. Kruse FE. Classification of ocular surface disease. In: Holland EJ, Mannis MJ (ed). Ocular surface disease: medical and surgical management. Springer-Verlag, New York, 2002 (pp.16-36).

14. Lopez-Garcia JS, Rivas L et al. Autologous serum eyedrops in the treatment of aniridic keratopathy. Ophthalmology 2008;115:262-7.
15. Nakamura T, Inatomi T et al. Phenotypic investigation of human eyes with transplanted autologous cultivated oral mucosal epithelial sheets for severe ocular surface diseases. Ophthalmology 2007;114:1080-8.
16. Nelson LB, Spaeth GL et al. Aniridia: a review. Surv Ophthalmol 1984;28:621-42.
17. Nishida K, Kinoshita S et al. Ocular surface abnormalities in Aniridia. Am J Ophthalmol 1995;120:368-75.
18. Tseng SC. Concept and application of limbal stem cells. Eye 1989;3:141-57.
19. Dua HS, Gomes JA et al. The amniotic membrane in ophthalmology. Surv Ophthalmol 2004;49(1):51-77.
20. Gatinel D, Hoang-Xuan. Le déficit en cellules souches limbiques. J Fr Ophthalmol 2000;23:718-28.
21. Edén U, Fagerholm P et al. Pathologic epithelial and anterior corneal nerve morphology in early-stage congenital aniridic keratopathy. Ophthalmology 2012;119(9):1803-10.
22. Collinson JM, Chanas SA et al. Corneal development, limbal stem cell function, and corneal epithelial cell migration in the Pax6 (+/-) mouse. Invest Ophthalmol Vis Sci 2004;45:1101-8.
23. Holland EJ, Djalilian AR, Scwartz GS. Management of aniridic keratopathy with keratolimbal allograft: a limbal stem cell transplantation technique.
Ophthalmology 2003;110:125-30.
24. Brandt JD, Casuso LA, Budenz DL. Markendly increased central corneal thickness and unrecognized finding in congenital Aniridia. Am J Ophthalmol 2004;137:348-50.
25. Elder MJ, Hiscott P, Dart JK. Intermediate filament expression by normal and diseased human corneal epithelium. Hum Pathol 1997;28:1348-54.
26. Donisi PM, Rama P et al. Analysis of limbal stem cell deficiency by corneal impression cytology. Cornea 2003;22:533-8.
27. Espana EM, Di Pascuale MA et al. Characterization of corneal pannus removed from patients with total limbal stem cell deficiency. Invest Ophthalmol Vis Sci 2004;45:2961-6.
28. Singh R, Joseph A et al. Impression cytology of the ocular surface. Br J Ophtalmol 2005;89:1655-9.
29. Patel DV, Sherwin T, McGhee CN. Laser scanning in vivo confocal microscopy of the normal human corneoscleral limbus. Invest Ophthalmol Vis Sci 2006;47(7):2823-7.
30. Shortt AJ, Secker GA et al. Ex vivo expansion and transplantation of limbal epithelial stem cells.
Ophthalmology 2008;115(11):1989-97.
31. Miri A, Alomar T et al. In vivo confocal microscopic findings in patients with limbal stem cell deficiency. Br J Ophthalmol 2012;96(4):523-9.
32. Rivas R, Murube J. Impression cytology study of dry eyes in patients with congenital Aniridia. Arch Soc Esp Oftalmol 2003;78(11):615-22.
33. Quinto GG, Campos M, Behrens A. Autologous serum for ocular surface diseases. Arq Bras Oftalmol 2008;71:47-54.
34. Dua HS, Azuara-Blanco A. Limbal stem cells of the corneal epithelium. Surv Ophthalmol 2000;44:415-25.
35. Grueterich M, Tseng SC. Ex vivo expansion of limbal epithelial stem cell: amniotic membrane serving as a stem cell niche. Surv Ophthalmol 2003;48:631
36. Tiller AM, Odenthal MT et al. The influence of keratoplasty on visual prognosis in aniridia: a historical review of one large family. Cornea 2003;22(2):105-10.
37. Holland EJ, Schwartz GS. The evolution of epithelial transplantation for severe ocular surface disease and proposed classification system. Cornea 1996;15:549-56.
38. Daya SM, Watson A et al. Outcomes and DNA analysis of ex vivo expanded stem cell allograft for ocular surface reconstruction. Ophthalmology 2005;112(3):470-7.
39. Henderson TR, Coster DJ, William KA. The long term outcome of limbal allografts: the search for surviving cells. Br J Ophthalmol 2001;85:604-9.
40. Sharpe JR, Daya SM et al. Survival of cultured allogeneic limbal epithelial cells following corneal repair. Tissue Eng 2007;13(1):123-32.

41. Strampelli B. Osteo-odontokeratoprosthesis. Ann Ottalmol Clin Ocul 1963;89:1039-44.
42. Falcinelli G, Falsini B et al. Modified osteo-odontokeratoprosthesis for treatment of corneal blindness: long-term anatomical and functional outcomes in 181 cases. Arch Ophthalmol 2005;123(10):1319-29.
43. Chammartin M, Goldblum D et al. Case report of osteo-odonto keratoprosthesis (Strampelli) and of Dacron keratoprosthesis (Pintucci). Klin Monatsbl Augenheilkd 2009;226:180-3.
44. Bakhtiari P, Chan C et al. Surgical and visual outcomes of the type I Boston Keratoprosthesis for the management of aniridic fibrosis syndrome in congenital aniridia. Am J Ophthalmol 2012;153(5):967-71.
45. Chan CC, Holland EJ. Infectious keratitis after Boston type 1 keratoprosthesis implantation. Cornea 2012;31(10):1128-34.
46. Kang JJ, de la Cruz J, Cortina MS. Visual outcomes of Boston keratoprosthesis implantation as the primary penetrating corneal procedure. Cornea 2012;31(12):1436-40.
47. Rudnisky CJ, Belin MW et al. Risk factors for the development of retroprosthetic membranes with Boston keratoprosthesis type 1: multicenter study results. Ophthalmology 2012;119(5):951-5.
48. Colby KA, Koo EB. Expanding indications for the Boston keratoprosthesis. Curr Opin Ophthalmol 2011;22(4):267-73.
49. Robert MC, Harissi-Dagher M. Boston type 1 keratoprosthesis: the CHUM experience. Can J Ophthalmol 2011;46(2):164-8.

Diagnosis and treatment of cataract in aniridia

Paolo Capozzi, Chiara Morini, Pasquale Vadalà

Aniridia may be associated with various abnormalities of lens transparency, position and morphology.

Altered lens transparency

Aniridia is associated with cataracts in 50-85% of patients. [1] In a recent study of 101 eyes, cataracts were present in 63%, of which 44% were congenital. Generally, cataracts begin to affect vision after the age of 5 years and most often between the age of 10 and 19 years. Cataracts with functional impairment of vision, and hence of prime consideration for surgery, was reported in 42% of cases (27 of 64 eyes). [3] Surgery is typically performed between the third and fifth decade of life, although earlier intervention in some cases has been reported. Of a total of 11 children (22 eyes) followed for congenital aniridia at the Temple Street Children's University Hospital, Dublin, between 1985 and 2007, cataracts developed in 14 eyes (72%) and half of the children affected underwent surgery at a mean age of 6.4 years. [3]

Altered lens position

Ectopia lentis, defined as displacement or malposition of the crystalline lens of the eye, is a rare disorder (4% of cases of congenital aniridia); [2] however, its prevalence varies widely, with 56% reported in some studies and 0% in others. This discrepancy may be explained by the difficulty in detecting minimal subluxation of the lens. [4,5] Subluxation has been associated with a higher risk of developing glaucoma. [6]

While the histological structure of the zonule appears normal, its chemical composition has not been fully elucidated. It is thought that zonular fiber weakening is secondary to hypoplasia of the ciliary body, which is associated with anomalies in the development of the angle which cause glaucoma. [2,4-6]

Altered lens morphology

Lens anomalies such as microphakia or microspherophakia are rare, [7] whereas greater curvature to the anterior than to the posterior surface is relatively frequent. Cases of congenital aphakia and lens resorption, [8,9] lenticular coloboma associated with retinal degeneration and glaucoma have been reported. [10]

Because of the rarity and variable manifestation of congenital aniridia, good evidence levels in the treatment of lens disorders in aniridia are lacking due to the impossibility of carrying out randomized controlled studies for comparing parameters such as surgical timing, cataract removal technique, type of intraocular lens (IOL), and options between combined or delayed intervention. Available studies do not provide a sufficient level of evidence that would support the eye doctor in deciding on optimal treatment.

The following paragraphs describe the clinical manifestations of lens disorders in congenital aniridia and the treatment options reported in the literature and compare the results from studies involving small patient series.

Questions and recommendations for diagnosis

Question 4A. In persons with aniridia, should lens position and transparency be evaluated and regular eye examinations carried out to promptly diagnose lens abnormalities?

Question 4B. Starting at what age and how often should lens examination be performed to promptly diagnose abnormalities?

A lens opacity may be found on diagnosis of aniridia or may develop later, sometimes even years after the primary diagnosis of aniridia.

Lens opacities

Small lens opacities noted at birth may not necessarily affect vision. In general, they are anterior or posterior polar opacities. The types of cataracts which can develop with age include: anterior (subcapsular, cortical with formation of a flat plaque, associated with coronary and pyramidal opacities); posterior (subcapsular or more intense petal- or coral-like patterns); presenile (nuclear or progressive cortical similar to senile cataracts but with early onset). [4,11]

Natural history of cataracts

Congenital opacities are generally asymptomatic; opacities with onset before 10 years of age affect vision in several ways and eventually require surgical removal between age 20 and 40.
In the majority of cases, cataracts appear after aniridia has already been diagnosed. Some are asymptomatic and are found on a regular eye exam or can cause a marked decrease in vision or an increase in glare symptoms, in which case cataracts manifest as one the complications secondary to aniridia, like glaucoma or aniridic keratopathy, and require surgery. [12]

Histology

The anatomopathological features of opacities in aniridia vary widely and are not specific to the disorder, whereas the anterior capsule of a cataractous lens is characterized by increased fragility and thinning especially in persons aged between 23 and 35 years. [13,14] The posterior capsule may show excretions resembling calcium degeneration in globus cells. [15]

Recommendation

GCP

The lens of neonates with aniridia should be carefully examined at birth, under narcosis if needed, to promptly identify abnormalities in lens transparency and position which could lead to the development of amblyopia. Follow-up controls should be performed at 6 months, and 3 and 5 years.

Questions and recommendations for treatment

Question 5. What are the surgical indications for cataracts in aniridia?

Surgical indications

Cataracts in an aniridic eye can be followed with watchful waiting or operated with removal of the opacity with or without implantation of an artificial lens. The choice of treatment will be dictated by various factors weighed on a case-by-case basis: patient age, type of cataract, postoperative visual prognosis (associated ocular manifestations) and risk of complications related to surgery. Surgery is indicated when the cataracts reduce vision and when the conditions of the optic nerve and retina strongly suggest improvement. In the preverbal stage of development, evaluation as to the degree the cataracts affect vision can only be presumptive and will depend on accurate examination of the position and density of the lens opacity and findings of electrodiagnostic testing of visual function, with the patient under narcosis or awake, evaluating case-by-case the presence of numerous variables that can affect the modality of the exam. Dense congenital opacities are considered for surgery according to the same criteria as for congenital cataracts. Cataract removal should be performed as early as possible, preferably within the first 8 weeks for monolateral congenital cataracts and within the first 10 weeks for bilateral cataracts.

The decision whether to operate will also depend on the risks specific to aniridic eyes: the literature reports new or worsening of ocular hypertonia following cataract surgery (gonioscopy, clinical history of the eye, inflammatory reaction after previous operations) [16] and an increase in corneal opacity, keratopathy, and endothelial failure. [17]

Aniridic eyes may develop inflammatory reactions or abnormal scarring. These considerations sometimes render the decision to operate difficult.

Various factors in preoperative assessment favor surgery: extraction of the cataractous lens may modify refraction and reduce the negative effects of aniridia by utilizing peripheral opacification of the lenticular capsule. This differs from the case of a displaced lens which will require removal even when opacities are absent, selecting the least injurious means to correct aphakia.

Preoperative work-up

The following examinations should be performed before the operation:

- Accurate examination of the lens: special attention should be paid to anchorage of the lens to the zonule. The lens may sometimes be weakly anchored without evident displacement. Expert surgeons recommend taking this into account when planning surgical treatment of cataracts. [2]
- Biometry and keratometry: if accurately performed in both eyes, these exams offer a sufficiently precise estimate of postoperative refraction since the mean error is 1.47±0.29 D and 80% of eyes have an error <2 D of the refraction target. [18]
- Ultrasound biometry: permits detailed study of corneal opacities, the conditions of the angle, and the type of cataracts; it can also aid in planning a better surgical strategy. [19]
- Evoked visual potentials (EVP) and electroretinography (ERG) performed with the patient under narcosis or awake are useful for gaining information about optic nerve and retina function[20, 21], which could be impaired due to congenital malformations or glaucomatous or amblyoptic damage. Test findings can provide an approximate prognosis of postsurgical reco very of vision.
- *Optical coherence tomography* (OCT) should be included in the preoperative work-up although it is difficult to perform in young children and in patients with less dense cataracts.

Surgical timing

Cataract surgery should be performed in eyes with good ocular tone preferably obtained by surgery (as in pediatric cases) and in the absence of intraocular inflammation.

Recommendation

V/C Given the risk of complications – often difficult to manage and potentially endangering vision – such as ocular hypertonia, choroid detachment, bleeding, retinal detachment, and corneal failure, cataract surgery should be considered a risky procedure in these patients and reserved for cases of advanced cataracts that severely reduce vision.

Question 6. What type of cataract surgery should be performed in aniridic patients aged under 8 years?

Cataract surgery may be difficult due to alterations in corneal transparency. To increase the visibility of the anterior segment, surgeons expert in pediatric ophthalmology advise applying a homogeneous layer of viscoelastic substance on the cornea and set the microscopy light and coaxial illumination to low intensity. Whatever the technique to enhance visualization of the anterior chamber, oblique illumination may also be considered[22, 23]. Mechanical deepithelization of the cornea is not advised since a deficit of stem cells associated with aniridia could inhibit epithelial turnover. [11]

Also advisable is to minimize limbal corneal access so as to avoid damaging the limbus due to the known deficit of stem cells in aniridia. Preferable is scleral tunneling, as worsening of corneal pannus has been reported to occur in almost 20% of cases of corneal incision of 170°. Also to be avoided is the use of IOL designed for aniridia as they are cumbersome and difficult to implant in small children. Postoperative peripheral opacification of the capsule acts as a "pupil" and reduces aniridic glare. Anterior capsule thinning and fragility are often encountered in young aniridic patients, a situation that the surgeon must take into account in order to prevent complications such as lost rhexis, posterior capsule rupture, and vitreal herniation[12, 14, 24, 25].

One study [13] advised the use of a heavy viscoelastic agent, staining of the capsule with trypan blue, execution of a small rhexis, maximal delicacy in maneuvering, and attention to chamber collapse. The use of an anterior chamber maintainer during cataract surgery in children makes the procedure safer and reduces most complications. In addition, it requires less use of viscoelastic material which could increase intraocular pressure. [26] Various studies have recommended slow motion phacoemulsification in cataract surgery in adults with aniridia. [24, 27]

Phacoemulsification should be performed with caution, reducing the flow, fluid turbulence, and avoiding pressure on the posterior capsule and the suspensor apparatus of the lens, since in eyes in which there was no evident subluxation prior to surgery, small fragile areas of the zonule may always be present.

In the majority of cases of congenital or infantile cataracts in aniridia, Dahan's technique, which employs an anterior chamber maintainer and a cannula for aspiration of lenticular material, followed by posterior capsulotomy and anterior vitrectomy in children under 8 years of age, is the most appropriate and least damaging. When capsulorhexis is too difficult to perform, vitrectomy may be used to gradually widen the aperture of the anterior capsule[26].

If manual phacoaspiration cannot be performed, vitrectomy is recommended instead.

In adults, cataracts are extracted by phacoemulsification. [28]

Recommendation

GCP For the extraction of congenital cataracts in children under 8 years of age, the recommended technique involves: anterior chamber maintainer, two parencenteses of the posterior limbus, the use of heavy viscoelastic substances to protect the endothelium, capsulorhexis, phacoaspiration, posterior capsulorhexis or capsulotomy with vitrectomy, and anterior vitrectomy.

Question 7. If, in addition to cataract surgery, another eye operation is necessary (e.g., for glaucoma or ocular surface disorders), should they be performed conjointly in the same session or separately?

Preferably, eye operations should be performed separately in order to avoid causing inflammatory reactions and abnormal fibrosis to which aniridic eyes are susceptible (e.g., trabeculotomy, trabeculectomy, and transplant).
Cataract and vitreoretinal eye surgery and cataract surgery performed in conjunction with corneal transplant in post-traumatic anirida carry complication rates similar to those reported for single procedures [29, 30] . Nonetheless, a conservative approach is more appropriate in eyes especially susceptible to inflammatory reactions and fibrosis[12] . When corneal opacities and cataracts are both present, cataract surgery should be performed before surgical treatment for corneal opacities. The decision of whether to proceed with corneal transplant should be taken only after an adequate postoperative period has elapsed and depending how vision is restored after the cataracts procedure. This recommendation derives from experience in the difficult management of corneal transplant in patients with aniridia and the higher complication rates in such patients. In other words, if vision improvement after cataracts surgery is satisfactory, the patient need not undergo keratoplasty. Only when corneal opacities impede sufficient visualization of the anterior chamber or render cataract surgery risky may it be more advisable to undergo keratoplasty and/or limbus transplant and delay cataracts surgery.

Recommendation

GCP When cataracts are associated with other eye conditions, cataracts surgery should be delayed after other procedures have been performed.

Questions and recommendations regarding complications

Question 8A. What are the complications associated with cataracts surgery?

Question 8B. Following cataracts surgery, which type of therapy is indicated and which control examinations are necessary?

The most common complications after cataracts surgery are:

- Postoperative hypertonia. This is most feared complication. Lens surgery can cause new hyper tonia or worsen preexisting glaucoma. This may be due to the presence of the IOL, especially if large, as it comes into contact with the uveal or trabecular structures. According to another hypothesis, aniridic eyes are more susceptible to developing glaucoma after an intraocular procedure, irrespective of the type of IOL, due to changes in the permeability of the hema to-ophthalmic barrier. [31] For these reasons, IOL designed for aniridia in children should not be used; instead, they may be reserved for adults without concomitant glaucoma.

- Progression of corneal epithelial failure. Cataract surgery may worsen corneal conditions. This risk, probably due to damage to the cornea during surgery or limbal stem cell deficiency, is not corroborated by specific studies but rather derives from surgeons' opinions. [17] Considering this risk, it may be very difficult for the surgeon to decide whether or not to perform cataract surgery.

• Progressive anterior fibrosis syndrome is a complication specific to aniridic eyes operated for cataracts. It refers to the formation of fibrotic plaque of variable density on the IOL, both anterior and posterior. These membranes may be so dense as to cause the IOL to dislocate. It is thought that the membranes form due to the vicinity or mechanical pressure of the IOL on the immature vessels of the iridial remnants. [32]

Recommendations

GCP Complications after cataracts surgery include postoperative hypertonia, progression of corneal epithelial failure, and progressive anterior fibrosis syndrome.

GCP During the postoperative period, a course of topical antibiotics and beta blockers for 20 days is recommended. Also recommended is subconjunctival cortisone application at the end of the procedure. Systemic administration for 8-10 days should be considered on a case-by-case basis.
Ocular tone should be regularly controlled, particularly monitoring of ocular pressure during the first 3 months following surgery, conjointly with conditions of the ocular surface, the anterior segment and the retina.

References

1. Nelson LB, Spaeth GL et al. Aniridia: a review. Surv Ophthalmol 1984;28(6):621-42.
2. Edén U, Beijar C et al. Aniridia among children and teenagers in Sweden and Norway. Acta Ophthalmol 2008;86(7):730-4.
3. Lee H, Meyers K et al. Complications and visual prognosis in children with aniridia. J Pediatr Ophthalmol Strabismus 2010;47(4):205-10.
4. Bakri S. Aniridia in the newborn. http://emedicine.medscape.com/article/1200592-overview (01-15-2013).
5. Ramesh T, Ramesh K et al. Development and cellular factors underlying corneal epithelial dysgenesis in the PAX6 +/- mouse model of aniridia. Exp Eye Res 2005;81:224-35.
6. Beattie PH. A consideration of aniridia, with a pedigree. Br J Ophthalmol 1947; 31(11):649-76.
7. Naithani P, Sinha A, Gupta V. Inherited partial aniridia, microcornea with high myopia and Bergmeister's papilla: a new phenotypic expression. Indian J Ophthalmol 2008;56(2):145-6.
8. Brauner SC, Walton DS, Chen TC. Aniridia. Int Ophthalmol Clin 2008;48(2):79-85.
9. Moreker M, Parikh R et al. Aniridia associated with congenital aphakia and secondary glaucoma. Indian J Ophthalmol 2009;57(4):313-4.
10. Doganay S, Emre S, Firat P. Bilateral aniridia lenticular coloboma and snowflake retinal degeneration. Ophthalmic Surg Lasers Imaging 2009;40(1):54-6.
11. Barraquer RI, Garcia Franco F et al. Protocolo de actuacion en pacientes con aniridia (Seccion IV, pp 114-51). Ene Ediciones, Madrid, 2008.
12. Lee H, Khan R, O'Keefe M. Aniridia: current pathology and management. Acta Ophthalmol 2008;86(7):708-15.
13. Schneider S, Osher RH et al. Thinning of the anterior capsule associated with congenital aniridia. J Cataract Refract Surg 2003; 29(3):523-5.
14. Hou ZQ, Hao YS et al. Clinical pathological study of the anterior lens capsule abnormalities in familial congenital aniridia with cataract. Beijing Da Xue Xue Bao 2005;37(5):494-7.
15. Zimmerman LE. The outflow problem in normal and pathologic eyes. Trans Am Acad Ophthalmol Otolaryngol 1966;70(5):767-76.

16. Roman S, Cherrate H et al. Implants a iris artificial dans la correction des aniridies ou des deficiencies iriennes fonctionnelles. J Fr Ophtalmol 2009(32):320-5.
17. Tornqvist K. Aniridia: sight-threatening and hard to cure. Acta Ophthalmol 2008;86(7):704-5.
18. Aslam SA, Wong SC et al. Implantation of the black diaphragm intraocular lens in congenital and traumatic aniridia. Ophthalmology 2008;115(10):1705-12.
19. El Shakankiri NM, Bayoumi NH et al. Role of ultrasound and biomicroscopy in evaluation of anterior segment anatomy in congenital and developmental cataract cases. J Cataract Refract Surg 2009;35(11):1893-905.
20. Tremblay F, Gupta SK et al. Effects of PAX6 mutations on retinal function: an electroretinographic study. Am J Ophthalmol 1998;126(2):211-8.
21. Vadala P, Capozzi P et al. L'aniridia nel neonato e nell'infanzia: gestione e trattamento. Viscochirurgia 2009.
22. Oshima Y, Shima C et al. Chandelier retroillumination assisted torsional oscillation for cataract surgery in patients with severe corneal opacita. J Cataract Refract Surg 2007;33:2018-22.
23. Neuhann IM, Neuhann TF. Cataract surgery and aniridia. Curr Opin Ophthalmol 2010;21(1):60-4.
24. Osher RH, Burk SE. Cataract surgery combined with implantation of an artificial iris. J Cataract Refract Surg 1999;25(11):1540-7.
25. Burk SE, Da Mata AP et al. Prosthetic iris implantation for congenital, traumatic, or functional iris deficiencies. J Cataract Refract Surg 2001;27(11):1732-40.
26. Dahan E. Pediatric cataract surgery. In Yanoff M, Duker JS (eds). Ophthalmology (3rd edition). Mosby, 2009.
27. Osher RH. Slow motion phacoemulsification approach. J Cataract Refract Surg 1993;19(5):667.
28. Capozzi P, Morini C et al. Corneal curvature and axial length values in children with congenital/ infantile cataract in the first 42 months of life. Invest Ophtalmol Vis Sci 2008; 49(11):4774-8.
29. Rossi T, Boccassini B et al. Combined pars plana vitrectomy and artificial iris diaphragm implant after globe rupture. Graefes Arch Clin Exp Ophthalmol 2009;247(4):439-43.
30. Phillips PM, Shamie N et al. Transscleral sulcus fixation of a small-diameter iris-diaphragm intraocular lens in combined penetrating keratoplasty and cataract extraction for correction of traumatic cataract, aniridia, and corneal scarring. J Cataract Refract Surg 2008;34(12):2170-3.
31. Reinhard T, Engelhardt S, Sundmacher R. Black diaphragm aniridia intraocular lens for congenital aniridia: long-term follow-up. J Cataract Refract Surg 2000;26(3):375-81.
32. Tsai JH, Freeman JM et al.A progressive anterior fibrosis syndrome in patients with postsurgical congenital aniridia. Am J Ophthalmol 2005;140(6):1075-9.

Secondary glaucoma in aniridia: diagnosis and treatment

Giorgio Marchini, Marco Toscani, Gabriele Vizzari

Questions and recommendations

Question 9. Which diagnostic procedures should be performed to evaluate secondary glaucoma in aniridia?

In 6-75% of cases, aniridic glaucoma may arise in late infancy, adolescence or sometimes adulthood due to iridogoniodysgenesis that blocks the drainage of aqueous humor from the anterior chamber angle. [1-4] This may co-exist with microstructural alterations of the cribrous lamina of the optic disc that render it more susceptible to damage from intraocular pressure. [5] Rare cases have been described of newborns with congenital glaucoma, buphthalmos and corneal edema associated with aniridia. [6-9]

Diagnostic workup includes gonioscopy, applanation tonometry, manual ultrasound biometry, examination of the optic disc (often performed under narcosis), and visual field examination when possible. Gonioscopy, in conjunction with ultrasound biomicroscopy (UBM) when corneal opacities are present or optical coherence tomography (OCT) of the anterior segment, will reveal the rudimentary stump of iris that has rotated anteriorly to progressively cover and obstruct the trabecular meshwork, and goniosynechiae. [10,11]

Applanation tonometry (according to Perkins or Goldman) to monitor intraocular pressure is essential for instituting and adjusting therapy; however, the method has intrinsic limitations, also because it often requires general anesthesia and correction with pachymetric measurements (usually above average). [5,12-14] Tonometry is combined with manual ultrasound biometry measurement of the anatomic axial length; an abnormally increased length due to anteroposterior weakening of the globe permits estimation of the progression of hypertony. [15]

Besides fundoscopy, more recent diagnostic procedures may be performed to evaluate the optic disc (GDx, Heidelberg retinal tomography [HRT], OCT imaging of the optic disc) depending on the patient's ability to cooperate, often limited in young patients, nystagmus beats, and loss of fixation. These techniques measure the nerve fiber thickness of the bundles converging on the optic disc, thus permitting early determination of loss of thickness.

Finally, visual field examination, unless difficult because of nystagmus and opacity of dioptric media, can reveal visual field deficits indicating glaucomatous changes or associated macular or disc anomalies in some cases. [16]

Follow-up care will include an annual eye examination to measure intraocular pressure and examination of the optic disc and the visual field, when possible.

Recommendation

V/A

The diagnostic workup and regular follow-up exams should include tonometry, ultrasound biometry and fundoscopy for optic disc examination. Patient age and compliance and nystagmus permitting, the workup should include GDx or HRT or OCT of the optic disc, and visual field examination.

Question 10. Which treatment procedures should be instituted in aniridic glaucoma?

The pertinent literature lacks studies meeting evidence-based medicine (EBM) criteria; cases series are usually too small to compare treatment effectiveness across studies and often without a control group. A comparative analysis did show, however, a high success rate for surgery with drainage implants (97%) followed by a considerable drop in the rates for protected filtering surgery (43%), parasurgery (31%), and pharmacotherapy (62%); of special mention is prophylactic goniotomy (89%). Accumulated evidence suggests that the treatment of choice is medical therapy with antiglaucomatous and miotic drugs, reserving parasurgery for less responsive cases (diode laser cyclophotoablation or cyclocryotherapy or the less effective argon laser trabeculoplasty) and/or surgery (trabeculectomy with or without antimetabolites, whereas trabeculotomy and goniotomy were reported to be less effective). [4,17-26] Prophylactic goniotomy has been suggested to be useful. [2, 27-30]

In refractory glaucoma, often occurring in patients with early onset of glaucoma, outcome after implantation of drainage devices (Molteno, Ahmed, Baerveldt valves) is satisfactory in 66-100% of cases. [11, 31-37]

Recommendation

V/B In aniridic glaucoma, the use of antiglaucomatous and miotic drugs without preservatives, when available, is recommended. When medical therapy is ineffective, surgical treatment options, in descending order of choice, include goniotomy, trabeculotomy with or without trabeculectomy and drainage valve implantation.

Table 1. Treatment of congenital glaucoma in aniridia. Type of surgery and outcome.

Author	Journal	Year	Cases (no. of patients)	Glaucoma + aniridia (no. of eyes)	Intervention		
					No.	Type	Successes*
Panda A et al.	*Indian J Ophthalmol*	1982	16	11	11 5 1	Drugs Cyclocryotherapy TRAB	6 1 1
Walton DS.	*Trans Am Ophthalmol Soc*	1986	16	28	28	Goniotomy (prophylaxis)	25 (89.3%)
Wiggins RE Jr, Tomey KF	*Arch Ophthalmol*	1992	10	17	20 2 2 15 6	Cyclocryotherapy Cyclodiode Trab TRAB Molteno Valve	5 0 0 1 5
Mandal AK et al.	*Ophthalmology*	1997	13	2	2	TRAB	2
Adachi M et al.	*Ophthalmology*	1997	16	29	12 6 17 14	Trab (first) Trab (second) TRAB/Goniotomy/ Molteno (first) TRAB/Goniotomy/ Molteno (second)	6 4 3 8
Filous A et al.	*Cesk Slov Oftalmol*	1998	11	22	22 9	Drugs Cyclocryotherapy or TRAB (?)	13 (59.1%) 6
Wagle NS et al.	*Ophthalmology*	1998	49	8	8	Cyclocryotherapy	0
Mandal AK et al.	*Ophthalmic Surg Lasers*	1999	29	2	2	TRAB	2
Chen TC, Walton DS.	*Arch Ophthalmol*	1999	33	55	55 6	Goniotomy (prophylaxis) Goniotomy + Drugs	49 (89.1%) 6
Esquenazi S, Amador S.	*Ophthalmic Surg Lasers*	2002	1	2	2	TRAB	2
Arroyave CP et al.	*Am J Ophthalmol*	2003	5	8	8	Valve Implant	8
Yalvac IS et al.	*J Cataract Refract Surg*	2004	1	1	1	Ahmed Valve	1
Menezo JL et al.	*Eur J Ophthalmol*	2005	8	4	3 3 1	Drugs Cyclodiode Ahmed Valve	1 2 1

Author	Journal	Year	Cases (no. of patients)	Glaucoma + aniridia (no. of eyes)	Intervention		
					No.	Type	Successes*
Lanzagorta-Aresti A et al.	*Ear J Ophthalmol*	2007	3	4	4	Ahmed Valve	4
Yu WH et al.	*Zhonghua Yan Ke Za Zhi*	*2008*	*8*	*5*	1 1 4	Drugs TRAB Cyclodiode	1 0 2
Low S et al.	*J AAPOS*	2008	25	1	*1* *22* *1*	*Trab+TRAB* *Drugs* *TRAB*	*1* *16 (72.7%)* *1*
Aslam SA et al.	*Ophthalmology*	*2008*	*35*	*40*	*3* *2*	*Cyclodiode* *Baerveldt Valve*	*2* *2*
Edén U et al.	*Acta Ophthalmol*	*2008*	*52*	*28*	*28* *8*	*Drugs* *TRAB or Molteno Valve*	*20 (71.4%)* *(?) ?*
Moreker M et al.	*Indian J Ophthalmol*	*2009*	*1*	*2*	*2* *2*	*Drugs* *TRAB*	*0* *2*
Diago T et al.	*Arch Soc Esp Oftalmol*	*2009*	*1*	*2*	*2*	*TRAB*	*2*
Kulkarni SV et al.	*J Glaucoma*	2010	8	4	4	Goniotomy	1
Zeppa L et al.	*Eur J Ophthalmol*	2010	15	1	1 1	TRAB Ahmed Valve	0 1
Lee H et al.	*J Pediatr Ophthalmol Strabismus*	2010	11	9	9 1 2 4 1 2 3	Drugs Cyclodiode Goniotomy TRAB Ahmed Valve Ahmed Valve (+revision) Ahmed Valve (+needling)	1 1 0 1 1 2 3
Terasaki H et al.	*Jpn J Ophthalmol*	2010	1	2	2	PPV + EndoCyclodiode	2
Park SH et al.	*Korean J Ophthalmol*	2010	31	31	31 6 3	Drugs TRAB Ahmed Valve	22 (71%) 6 3

TRAB denotes trabeculectomy; trab trabeculotomy; PPV pars plana vitrectomy

** Successful treatment outcome is defined as achievement of intraocular pressure < 21 mm Hg.*

The total number of interventions may be greater than the number of eyes because it includes the number of repeat surgeries for recurrences. Treatment was performed according to the order of validated therapy: medical therapy, parasurgery, perforating surgery, and drainage.

References

1. Gramer E, Reiter C, Gramer G. Glaucoma and frequency of ocular and general diseases in 30 patients with aniridia: a clinical study. Eur J Ophthalmol 2012;22(1):104-10.
2. Lee H, Khan R, O'Keefe M. Aniridia: current pathology and management. Acta Ophthalmol 2008;86(7):708-15.
3. Margo CE. Congenital aniridia: a histopathologic study of the anterior segment in children. J Pediatr Ophthalmol Strabismus 1983;20(5):192-8
4. Grant WM, Walton DS. Progressive changes in the angle in congenital aniridia, with development of glaucoma. Trans Am Ophth Soc 1974;72:207-28.
5. Dimasi DP, Burdon KP, Craig JE. The genetics of central corneal thickness. Br J Ophthalmol 2010;94(8):971-6.
6. Diago T, Harto M et al. Aniridia, congenital glaucoma and white corneas in a newborn baby. Arch Soc Esp Oftalmol 2009;84(11):573-6.
7. Khan AO, Aldahmesh MA, Al-Amri A. HeterozygousFOXC1 mutation (M161K) associated with congenital glaucoma and aniridia in an infant and a milder phenotype in her mother. Ophthalmic Genet 2008;29(2):67-71.
8. Lise-Schneider B, Calvas P et al. Glaucoma with aniridia and isolated congenital glaucoma in siblings: contribution and limits of genetics. J Fr Ophtalmol 2007;30(1):44-8.
9. Lee WB, Brandt JD et al. Aniridia and Brachmannde Lange syndrome: a review of ocular surface and anterior segment findings. Cornea 2003;22(2):178-80.
10. Engels BF, Dietlein TS et al. Ultrasound biomicroscopy diagnosis of congenital glaucoma. Klin Monatsbl Augenheilkd 1999;215(6):338-41.
11. Lee H, Meyers K et al. Complications and visual prognosis in children with aniridia. J Pediatr Ophthalmol Strabismus 2010;47(4):205-10.
12. Freedman SF. Central corneal thickness in children-does it help or hinder our evaluation of eyes at risk for glaucoma?. J AAPOS 2008;12(1):1-2.
13. Whitson JT, Liang C et al. Central corneal thickness in patients with congenital aniridia. Eye Contact Lens 2005;31(5):221-4.
14. Brandt JD, Casuso LA, Budenz DL. Markedly increased central corneal thickness: an unrecognized finding in congenital aniridia. Am J Ophthalmol 2004;137:348-50.
15. Dureau P. Congenital glaucoma and trabeculodysgenesis. Clinical and genetic aspects. J Fr Ophtalmol 2006;29(2):198-215.
16. Ho CL, Walton DS. Primary congenital glaucoma: 2004 update. J Pediatr Ophthalmol Strabismus 2004;41(5):271-88.
17. Low S, Hamada S, Nischal KK. Antimetabolite and releasable suture augmented filtration surgery in refractory pediatric glaucomas. J AAPOS 2008;12(2):166-72.
18. Brémond-Gignac D. Glaucoma in Aniridia. J Fr Ophtalmol 2007;30(2):196-9.
19. Kirwan JF, Shah P, Khaw PT. Diode laser cyclophotocoagulation: role in the management of refractory pediatric glaucomas. Ophthalmology 20z02;109(2):316-23.
20. Okada K, Mishima HK et al. Results of filtering surgery in young patients with aniridia. Hiroshima J Med Sci 2000;49(3):135-8.
21. Wallace DK, Plager DA et al. Surgical results of secondary glaucomas in childhood. Ophthalmology 1998;105(1):101-11.
22. Wagle NS, Freedman SF et al. Long-term outcome of cyclocryotherapy for refractory pediatric glaucoma. Ophthalmology 1998;105(10):1921-6.
23. Filous A, Odehnal M, Brůnová B. Results of treatment of glaucoma associated with Aniridia. Cesk Slov Oftalmol 1998;54(1):18-21.
24. Adachi M, Dickens CJ et al. Clinical experience of trabeculotomy for the surgical treatment of aniridic glaucoma. Ophthalmology 1997;104(12):2121-5.
25. Wiggins RE Jr, Tomey KF. The results of glaucoma surgery in Aniridia. Arch Ophthalmol 1992;110(4):503-5.
26. Panda A, Sood NN, Agarwal HC. Management of secondary glaucoma in Aniridia. Indian J Ophthalmol 1982;30(4):311-3.
27. Swanner JC, Walton DS, Chen TC. Prevention of aniridic glaucoma with goniosurgery. Int Ophthalmol Clin 2004;44(1):67-71.
28. Chen TC, Walton DS. Goniosurgery for prevention of aniridic glaucoma. Arch Ophthalmol 1999;117(9):1144-8.

29. Chen TC, Walton DS. Goniosurgery for prevention of aniridic glaucoma. Trans Am Ophthalmol Soc 1998;96:155-65.
30. Walton DS. Aniridic glaucoma: the results of gonio-surgery to prevent and treat this problem. Trans Am Ophthalmol Soc 1986;84:59-70.
31. Zeppa L, Romano MR et al. Sutureless human sclera donor patch graft for Ahmed glaucoma valve. Eur J Ophthalmol 2010;20(3):546-51.
32. Park HY, Lee NY, Park CK. Risk factors of shallow anterior chamber other than hypotony afterAhmed glaucoma valve implant. J Glaucoma 2009;18(1):44-8.
33. Brauner SC, Walton DS, Chen TC. Aniridia. Int Ophthalmol Clin 2008;48(2):79-85.
34. Arroyave CP, Scott IU et al. Use of glaucoma drainage devices in the management of glaucoma associated with aniridia. Am J Ophthalmol 2003;135(2):155-9.
35. Beauchamp GR, Parks MM. Filtering surgery in children: barriers to success. Ophthalmology 1979;86(1):170-80.
36. Chen TC, Bhatia LS, Walton DS. Ahmed valve surgery for refractory pediatric glaucoma: a report of 52 eyes. J Pediatr Ophthalmol Strabismus 2005;42(5):274-83.
37. Trigler L, Proia AD, Freedman SF. Fibrovascular ingrowth as a cause of Ahmed glaucoma valve failure in children. Am J Ophthalmol 2006;141(2):388-9.

Alterations of the retina and the optic nerve in aniridia

Antonino Romanzo

Genetic basis of alterations of the retina and the optic nerve in aniridia

In the vertebrate embryo, the eye is formed from multiple embryonic tissues interacting with each other in close connection: the neuroepithelium, the ectoderm, and the extraocular mesenchyme derived from the neural crest and the mesoderm. The retinal pigment epithelium plays a central role in eye development and retinal stratification as it regulates photoreceptor differentiation. Loss of the retinal pigment epithelium or genetic defects underlying its loss can result in microphthalmos, coloboma, and retinal alterations. PAX6 gene mutations may interfere with differentiation of the pigment epithelium. [1,2]

Malformations of the retina and the optic nerve in aniridia

Various malformations of the retina and the optic nerve may be associated with aniridia. Foveal hypoplasia/aplasia appears to the principal cause of visual deficit and nystagmus. Mutations in the PAX6 gene have been implicated in the development of the central retina, though they must be associated with a deficit in melanin synthesis to cause alterations in the foveal area. The PAX6 gene is also involved in retinal vasculature.

A comparative study on retinal albinism and aniridia demonstrated that the retinal vessels in the foveal area are less numerous and shorter in aniridia. [3] The study also showed that this alteration in retinal vasculature does not cause optic nerve hypoplasia. On opthalmoscopy, foveal alterations may manifest as lack of depression and reduction of the characteristic reflex. Optic nerve hypoplasia may not necessarily be the main cause of visual deficit, as the optic chiasm has been shown to develop independently of the fovea. [3] Other studies have found PAX6 mutations in diverse alterations of the optic nerve. [4,5]

In routine practice, co-existing foveal and optic nerve hypoplasia is commonly encountered in patients with aniridia.

Visual deficits associated with alterations of the retina and the optic nerve in aniridia

Visual deficit in aniridic patients is always severe and represents the sum of disorders affecting the cornea, crystalline lens, fovea and optic nerve. Foveal hypoplasia is associated with a reduced number of photoreceptors, with subsequent worsening of visual deficit. [6]

Nystagmus results from foveal hypoplasia. Nearly all patients present with elevated myopia, a further factor in reduced vision.

Rare cases of complete retinal detachment have been described. Though this has not been linked to genetic causes, lipid accumulations in the outer retinal periphery have been observed in such patients. [7,8]

Questions and recommendations

Question 11A. Following a diagnosis of aniridia, which diagnostic examinations are recommended for detecting alterations of the fovea and the optic nerve?

Question 11B. Which follow-up examinations are recommended and how often should they be performed?

Visual acuity assessment, though a cornerstone procedure in ophthalmology, may be impossible to perform in aniridic patients with foveal and optic nerve malformations. Ophthalmoscopy with a direct or indirect ophthalmoscope is the procedure of choice for fundus examination. Other

diagnostic tests, though not always practical in pediatric patients, include evoked visual potential (EVP), electroretinography (ERG), optical coherence tomography (OCT), and fluorangiography. When possible, examination with a panfundus lens may be useful for acquiring images of the retina and the optic nerve.
Electrodiagnostic testing (ERG, EVP) can aid in the assessment of retina and optic nerve function. Because of their complexity and invasiveness, these procedures may not be practical in children; and because of the numerous variables involved, performing such tests with the patient under narcosis or awake will need to be evaluated case-by-case.
OCT can confirm hypoplasia of the fovea and the optic nerve, thus providing measurable indicators for assessing the condition. Manual devices are commercially available for performing OCT with the patient under narcosis.
Fluorangiography is used to evaluate the retinal vasculature. Owing to its complexity and invasiveness, the produce is routinely performed under narcosis.
Precisely because accurate assessment of the entire visual apparatus is so important in aniridia and because many exams can only be performed with the patient under narcosis, they should be carried out in a single session.

Recommendations

GCP Diagnostic assessment of foveal and optic nerve alterations should include:
Ophthalmoscopy to detect changes in the retinal periphery and the foveal area.
ERG, EVP, OCT and fluorangiography to evaluate function and hypoplasia of the retina and optic nerve, and retinal vasculature, respectively.

GCP Images of the retina and optic nerve should be acquired with the use of a panfundus lens.

GCP Examinations should be performed at patient assessment, preferably within the first 3 months of life.

GCP Given the complexity and invasiveness of the procedures and the need for patient cooperation in order to obtain reliable results, testing in children should be performed under narcosis and preferably during a single session. In electrodiagnostic testing (ERG and EVP), owing to the numerous variables that can influence test modality, carrying out a procedure with the patient under narcosis or awake should be decided case-by-case. During follow-up, children with aniridia and alterations of the retina and optic nerve should undergo clinical eye exams every 3 months and diagnostic eye tests once a year.

References

1. Fuhrmann S. Eye morphogenesis and patterning of the optic vesicle. Curr Top Dev Biol 2010; 93:61-84.
2. Gupta SK, De Becker I et al. Genotype/phenotype correlations in aniridia. Am J Ophthalmol 1998;126(2);203-10.
3. Neveu MM, Holder GE et al. Optic chiasm formation in humans is independent of foveal development. Eur J Neurosci 2005; 22(7):1825-9.
4. McCulley TJ, Mayer K et al. Aniridia and optic nerve hypoplasia. Eye 2005;19(7):762-4.
5. Matsushima D, Heavner W, Pevny LH. Com binatorial regulation of optic cup progenitor cell fate by SOX2 and PAX6. Development 2011; 138(3);443-54.
6. Tremblay F, Gupta SK et al. Effects of PAX6 mutations on retinal function: an electroretinographic study. Am J Ophthalmol 1998;126(2);211-8.
7. Hama Y, Hirakata A et al. Retinal detachment with giant oral dialysis in an eye with congenital aniridia. Jpn J Ophthalmol 2010;54(1):105-7.
8. Lee H, Meyers K et al. Complications and visual
prognosis in children with aniridia. J Pediatr Ophthalmol Strabismus 2010;47(4):205-10.

Therapeutic and rehabilitation strategies in children with aniridia

Luisa Pinello

Introduction

Aniridia causes severe visual impairments. In developed countries, 20% of children with ocular malformations have low vision due to aniridia. [1-4] Numerous factors contribute to low vision: greater amount of light rays entering the eye; corneal and lens opacities; glaucoma; foveal and optic nerve hypoplasia; [5-7] photophobia; nystagmus, and high myopia. [8] Best-corrected visual acuity (BCVA) is generally low: in a study involving 124 adults, [2] the mean BCVA was 0.2 (<0.3 in 80% and <0.1% in 18% of cases). In another study in adults, the mean BCVA was 0.19, [9] while a study in 12 children reported a BCVA of 0.22±0.15. [10]

Measurement of visual acuity is challenging in children, especially in infants (0-3 years) and those with mental retardation (children with WAGR or Gillespie syndrome). [9] In such patients, visual acuity can be evaluated with preferential look testing, most commonly performed with Teller acuity cards. [11] Starting from the 3 years of age visual acuity can be evaluated with ETDRS logMAR charts:in toddlers (3-4 years), it can be evaluated with LEA tests [12,13]; in preschoolers (4-6 years) visual acuity is tested using Snellen letter E charts or letter charts in children aged 6 years and older. [14] Macular hypoplasia is evaluated by indirect ophthalmoscopy, eventually confirmed by OCT. [15]

The aim of treatment is to manage the eye disorders that impair visual function, improve visual performance though rehabilitation strategies and aids, reduce or relieve symptoms, and, in patients with low vision, to promote learning, communication and daily living safety skills, and to foster social and scholastic participation and the child's development and overall well-being. [12,16] Defining the criteria to attain these goals can be a useful way to reduce the impact low vision has on children with aniridia.

In the following paragraphs, the appropriateness (i.e., the efficacy and safety) of available therapeutic approaches to reduce visual disability in children with aniridia is evaluated.

Questions and recommendations

Question 12. Which elements should be evaluated for defining therapeutic-rehabilitation options in children with aniridia?

The therapeutic-rehabilitation approach starts with elements from case history and is based on accurate assessment of visual function.

In addition to family history and findings from physical and diagnostic examinations, the case history will include information on visual function. For example, parents will note glare and photophobia in very young children unable to describe these phenomena, which may be caused by exposure to outdoor light (mild photophobia), indoor light (moderate photophobia), or even dimly lit environments (severe photophobia). Other essential information concerns near, intermediate, and distance vision, mobility and orientation outdoors, communication, environmental problems at home and at school, and alterations or delays in development. [7,12,16]

For planning rehabilitation therapy, complete ophthalmologic evaluation will also include assessment of visual function by measuring BCVA using tests appropriate for the child's age and ability to cooperate, [7,11,13,14,17] near visual acuity by means of octotypes and related letter height, [18] fixation, eye movement, head positioning, nystagmus and photophobia.

Recommendation

GCP Defining therapeutic and rehabilitation options that will preserve visual function should be based on accurate history taking, evaluating for the presence of photophobia, and measurement of visual acuity using tests appropriate for the child's age and ability to cooperate.

Question 13. How should photophobia be treated?

Photophobia refers to an abnormally low tolerance to light. Exposure to light produces intense eye irritation and discomfort which elicits squinting or closing the eyes or other light avoidance behaviors. [19] The main cause of photophobia is glare: one type of glare impairs vision, reducing the perception of contrast between objects and background and making visual tasks difficult to perform (due to corneal or lens opacities); the other type produces eye irritation or discomfort but without reducing visual function.

Treatment for glare that impairs vision involves adopting precautions such as: avoiding bright light; providing for adequate room illumination with indirect or suffuse light; not viewing video screens unless environmental illumination is adequate; not placing light sources at eye level; using shaded lamps; not using spotlights for reading; wearing sunglasses. [20] Treatment for glare from sunlight that produces eye irritation and discomfort includes: wearing a wide-brimmed hat or cap; avoiding bright or reflecting surfaces; avoiding abnormal reflections; reducing the glare from foliage, book pages, desks and blackboards. The use of sunglasses or photochromic glasses helps to reduce the intensity of light reflecting off windows, mirrors, and smooth white or brightly colored surfaces. Sunglasses with UV filters serve a dual purpose: [21] to reduce glare and photophobia and to protect against the harmful effects of increased UV light rays entering the eyes. Also recommended is the use of spectral filters (511-585 nm), [22] though, because of the rarity of aniridia, there is little published evidence supporting their use. Nonetheless, they should be prescribed as needed for outdoor and indoor use according to wearer comfort. [21] In younger children, they should be used depending on how the child reacts on exposure to bright light.

Recommendations

GCP To avoid glare, preventive measures include providing protection against bright light and good room illumination with indirect suffuse lighting, and wearing sunglasses and a wide-brimmed cap. Behaviors to be avoided include: viewing video screens without adequate background illumination; light sources set at eye level; exposure to bright reflection; spotlights instead of shaded lamps for reading.

GCP The use of spectral filters is recommended to reduce glare.

V/B Published evidence reports improvement in photophobia and glare when these prevention measures are adopted.

Question 14. How efficacious are available therapeutic approaches to correcting refraction defects in aniridia?

Children with aniridia often present with severe refraction defects, particularly elevated myopia[23] in up to 64% of cases[8].

Prescription eyeglasses or contact lenses should be used to correct refraction defects [8,23] as measured with fixed or preferably portable autorefraction under cycloplegia[7] .The objective of the prescription is to improve BCVA, even in persons with severely low vision, to increase depth perception and reduce visual impairment, if present, within the first year of life. One might think that cycloplegia (1 drop of cyclopentate instilled every 5 minutes, then refraction after 30-45 minutes) is not useful because the iris is either absent or reduced in size, however, a certain degree of accommodation persists. Optical treatment of high myopia in aniridia should be meticulous[8,23]. Amblyopia, if present, should be treated with eye patching: children with structural asymmetries often experience improvement in visual acuity after treatment for amblyopia. [5,24]

Consensus is lacking as to whether contact lenses should be preferred for optical correction of refraction defects; however, they are indicated in the treatment of elevated or anisiometric defects (hydrogel contact lenses), as they provide for a better visual field and are highly recommended in aphakia surgery (silicone elastomere contact lenses). [7] The distinct advantages to contact lenses reside in their morphofunctional and cosmetic aspects (38% hydrogel [HEMA] contact lenses) and nontoxic tints. Furthermore, contact lenses form an artificial pupil (5 mm) that attenuates photophobia, glare from above, and nystagmus, protect against UVA and UVB rays, facilitate the use of monocular magnifying aids for distance vision, and improve vision, comfort and quality of life. [24,25]

The disadvantages of contact lenses include the increased risk of infections and corneal damage in patients with aniridic keratopathy due to altered stem cell production, resulting in longer time to healing of infection or corneal scarring. Cosmetic contact lenses may also cause vision problems in dim light or at night because the pupil does not change size to accommodate to darkness. They require extra care and attention, which parents will need to tend to in small children. They also require more frequent monitoring than eyeglasses and are not as effective as eyeglasses in correcting astigmatism, particularly if severe. [7]

Recommendations

GCP Refraction defects can be corrected with eyeglasses or contact lenses following autorefraction under cycloplegia.
Contact lenses should be used with caution in children with aniridia due to alterations in lubrication and the corneal epithelium.
Consensus is lacking as to whether contact lenses are preferable for optic correction of refraction defects. Contact lenses are particularly indicated in high myopia and anisometry.
Amblyopia, if present, should be treated with eye patching.

V/B Silicone contact lenses are recommended in aphakia surgery.

V/B The use of contact lenses for morphofunctional and cosmetic purposes should be evaluated case-by-case, weighing the risks and benefits.

GCP Eye examinations should be performed every 6 months, more often if amblyopia is present. More frequent exams are also recommended if corneal or crystalline lens disorders or glaucoma are present, depending on the individual case and related problems.

Question 15. Which visual rehabilitation treatment is appropriate in children with aniridia?

Low vision in children

Low vision refers to a condition in which, because of an eye or, more rarely, a neurologic disorder, a person has lost visual independence in carrying out activities of daily living. In children with aniridia, low vision may be due to one or a combination of multiple factors: foveal and optic nerve hypoplasia; nystagmus; amblyopia; cataracts; glaucoma; and corneal opacities (aniridic keratopathy). [5]

Visual function is essential for the development of the senses and perception, learning and interpretation of the world surrounding the child. In fact, 80% of learning is based on vision. Furthermore, low vision in childhood has a significant impact on the development of motor, neurological, cognitive and relational skills, potentially restricting the range of experience and information the child is exposed to. Low vision concurrent with other disabilities, particularly impaired hearing or intellectual development, compounds the negative effects each produces, worsening the degree of overall impairment. [26]

Low vision is difficult to define in children as their visual system is still developing and measuring it presents particular challenges, especially in very young and multidisabled children. [17] The World Health Organization (WHO) defines low vision or blindness according to 6 categories of severity according to visual acuity and visual field. Low vision is defined as visual acuity <3/10 in the better eye and with best correction or a visual field <60°.

Somewhat differently, Italian law (Law 138/2001) [27] defines low vision or blindness according to 5 categories. Eligible for legal benefits are persons with extremely low vision (remaining vision <1/10 in both eyes or in the better eye, also with best correction, or those with remaining peripheral binocular vision <30%), those with partial blindness (remaining vision <1/20 in both eyes or in the better eye, also with best correction, or those with remaining peripheral binocular vision <10%), and those with total blindness (complete lack of vision in both eyes, only perception of shadows and light or hand movements by both eyes or the better eye, or remaining peripheral vision <3%).

Importantly, while the WHO classification and Italian legislation consider only two parameters, visual acuity and visual field, the management of children with low vision will need to take several other factors into account that determine vision quality: gaze; fixation; tracking; perception of contrast and depth; glare and adaptation, and accommodation. [12]

Vision rehabilitation

Unlike persons with total blindness, those with low vision have remaining vision that can and must be trained to the fullest of their capacities. In children, because the maturation process is not yet complete, their development must be aided. [7,26] Though they may be unable to perform many activities and can experience problems in social relationships, they can be helped through the use of adaptive/assistive devices (see section on adaptive/assistive devices below) combined with skills strategies to enhance remaining vision.

Just as the choice of therapy hinges on correct diagnosis, so too ophthalmologic and systemic functional assessment will inform an integrated multidisciplinary rehabilitation plan that is holistic in its approach to a child with aniridia. Management of children with low vision is problematic: glare; reduced distance vision; reduced near vision due to foveal hypoplasia; fatigue; accommodation spasms; blurry vision; difficulty in distinguishing colors; anomalous head posture (compensatory positioning); anomalous eye movement (nystagmus); and the absence of stereopsis.

Treatment of aniridia-related problems and rehabilitation of visual function oriented to improving the child's quality of life all have a positive effect on learning, communication and activities of daily living, thus facilitating insertion and participation in community life and enhancing the child's development and overall well-being. [7,12,16,26]

Rehabilitation methods are recommended which are aimed at reducing glare, improving optic correction (see Question 14 above), and facilitating environmental skills, together with modifying the home environment, adjusting contrast (to minimize problems with stereoptic vision), providing for adequate lighting and ergonomic devices to correct posture and cope with nystagmus (inclined desktop, reading lectern, ergonomic chair), will all enhance the child's independent mobility at home and at school.
Also recommended is skills learning in orientation and daily living safety, mobility coaching, and personal independence or other personalized interventions. Furthermore, psychological support is recommended to assist children with delayed development and behavior disorders [7,8] resulting from the psychological effects of low vision on self image and self esteem, appearance-related dissatisfaction with assistive/adaptive devices or other causes, psychiatric problems and mental retardation (WAGR and Gillespie syndromes). [2,9]
Parental support is fundamental, which can be enlisted starting from a frank discussion of the diagnosis, the child's visual prognosis, and treatment and rehabilitation options, and must be sustained through support provided to the parents directly or parent groups. [7]
While a generalized scheme of preferences and practices in rehabilitation may respond to the needs of the majority children with aniridia, it cannot cover all circumstances. This means that rehabilitation must be personalized to the individual child who will have different needs that require specific responses.

Adaptive/assistive devices
Visual rehabilitation encompasses the use of electronic/optic and nonoptic devices according to the person's cognitive development. Choices from among the vast range of available devices will follow on from decisions of how best to provide an efficacious and personalized response to the child's needs, appropriate for age and cognitive development, and remaining or potential visual ability. [7,10,12,21] Prescription of a device will be based on accurate diagnostic assessment of organic abnormalities and visual function, after having corrected the underlying refraction defect and after a trial phase and training in the use of the device.
Devices are provided to patients through prescription by an ophthalmologist working within the national health service (NHS), which is then authorized by the local health district; the device is supplied and tested to verify proper functioning and use. [28] Devices can be prescribed as specified under the provisions of Decree Law (27 August 1999); they include optic devices (lenses, contact lenses, magnifiers for near and distance vision, etc.), electronic/computerized equipment and other aids (e.g., reading lectern). [28] The law lists which types of optical and electronic equipment is provided through the NHS by prescription from a specialist eye doctor, which will state the diagnosis, the type of aid and related codes, variability over time, duration of application, and the purpose of rehabilitation.

Table 2. Types of adaptive/assistive devices

Optic devices for distance vision	Contact lenses (for aniridia, aphakia due to cataracts), spectral filter lens to protect against harmful light radiation or reduce glare, telescopic magnifiers for distance vision (Galilean, Keplerian), monocular magnifier, portable eyeglass- or head-mounted telecamera with portable monitor or LCD
Systems for near vision	Magnifying lenses; aplanatic bifocal magnifying lenses; Galilean and Keplerian telescopes; monocular or binocular hypercorrection eyeglasses (prisms); prismatic binocular eyeglasses for myopia
Aids for the blind	Braille printer; text-to-speech reader; Braille writing tablet; Braille display; Braille typewriter
Other aids	Inclined desktop; reading lectern; ergonomic chair; overhead lighting
Electronic devices and technologies	Fixed video magnifier or CCTV systems; portable video magnifier; magnification software for PC; text recognition and reading system with scanner and OCR-ICR application software

The use of a video magnifier (CCTV systems) should be considered depending on the child's cognitive and hand-eye coordination skills, especially if the child is multidisabled or intellectually delayed. In individual cases a video magnifier can be used in rehabilitation for stimulating responses to enlarged images. Prior to prescription, the child's visual field should be tested because a narrow visual field renders use of the device difficult. [7,21]

Recommendations

GCP In children with aniridia, an integrated rehabilitation program will aim to facilitate the development of motor, neurological, cognitive and relational skills.

GCP Visual rehabilitation should include strategies to reduce glare, improve optic correction, and modify the environment by enhancing contrasts (to minimize problems with stereoptic vision), providing for adequate illumination and ergonomic aids to correct posture and cope with nystagmus (inclined desktop, reading lectern, ergonomic chair).

GCP Visual rehabilitation should comprise the use the electronic/optic and nonoptic devices. To improve near vision, in children with macular hypoplasia, the use of optic and electronic magnifying systems for near vision should be used: fixed or portable video magnifier; PC with large-print keyboard and software program; screen reader; text-to-speech reader; audiobooks; tactile markers; and Braille reading and writing.

V/B To improve distance vision, the use of optic magnifying systems is recommended.

GCP Skills teaching in orientation, mobility, daily living safety and independence appropriate to the child's individual needs is recommended.

GCP Psychological evaluation and support is recommended in children with low vision and aniridia because of the effect low vision can have on self image and self esteem, and appearance-related problems due to the use of assistive devices or other.

GCP Parents should be provided with support starting from the diagnosis of aniridia; the diagnosis should be discussed frankly, offering information about the disorder, the child's visual prognosis, and appropriate therapeutic-rehabilitation approaches.

GCP Cognitive, behavioral and neuropsychological assessment should be performed for the various syndromes (WAGR and Gillespie syndrome) associated with aniridia.

References

1. Alagaratnam J, Sharma TK et al. A survey of visual impairment in children attending the Royal Blind School, Edinburgh using the WHO childhood visual impairment database. Eye 2002; 16(5):557-61.
2. Edén U, Beijar C et al. Aniridia among children and teenagers in Sweden and Norway. Acta Ophthalmol 2008;86(7):730-4.
3. Hatton DD, Schwietz E et al. Babies Count: the national registry for children with visual impairments, birth to 3 years. J AAPOS 2007; 11(4):351-5.
4. World Health Organization. International classification of impairments, disabilities and handicaps. WHO, Geneve, 1980.
5. Mayer KL, Nordlund ML et al. Keratopathy in congenital aniridia. Ocul Surf 2003; 1(2):74-9.
6. Schroeder HW, Orth U et al. Hereditary foveal hypoplasia - clinical differentiation. Klin Monbl Augenheilkd 2003;220(8):559-62.
7. Taylor D. Paediatric ophthalmology (3rd edition). Blackwell Science, London, 2005 (pp 57-76; 126-31; 244-65; 1098-102).
8. Valenzuela A, Cline RA. Ocular and nonocular findings in patients with aniridia. Can J Ophthalmol 2004;39(6):632-8.
9. Edén U, Iggman D et al. Epidemiology of aniridia in Sweden and Norway. Acta Ophthalmol 2008;86(7):727-9.
10. Pinello L, Mazzarolo M et al. Aniridia congenita: follow-up clinico ed esiti funzionali visivi. Abstract book 25° Congresso nazionale Società italiana di oftalmologia pediatrica, Ostuni, 12-14 giugno 2008.
11. Clifford-Donaldson CE, Haynes BM, Dobson V. Teller Acuity Card norms with and without use of a testing stage. J AAPOS 2006;10(6):547-51.
12. Hyvärinen L. Considerations in evaluation and treatment of the child with low vision. Am JOccup Ther 1995;49(9):891-7.
13. Rydberg A, Ericson B et al. Assessment of visual acuity in children aged 1 1/2-6 years, with normal and subnormal vision. Strabismus 1999;7(1):1-24.
14. Williams MA, Moutray TN, Jackson AJ. Uniformity of visual acuity measures in published studies. Invest Ophthalmol Vis Sci 2008;49(10):4321-7.
15. Holmström G, Eriksson U et al. Optical coherence tomography is helpful in the diagnosis of foveal hypoplasia. Acta Ophthalmol 2010;88(4):439-42.
16. Colenbrander A, Fletcher D. Ipovisione e riabilitazione visiva. Verduci Editore, Roma, 1994.
17. Battistin T, Lanners J et al. Visual assessment in multidisabled infants. International congress series 2005;1282:21-5.
18. Limoli PG, D'Amato L et al. Il corpo stampa quale standard internazionale per la valutazione della funzionalità visiva. In Argomenti di ipovisione. Fabiano Gruppo Editoriale, Canelli, 2000 (pp 163-71).
19. Martin EA. Oxford concise colour medical dictionary. Oxford University Press, 1998 (p. 507).
20. McMullan R. Environmental science in building (4th edition). Palgrave Macmillan, 1998.
21. Zingirian M, Gandolfo E. Ipovisione. Nuove frontiere dell'oftalmologia. Fabiano Gruppo Editoriale, Canelli, 2002.
22. Rosenblum YZ, Zak PP et al. Spectral filters in low-vision correction. Ophthalmic Physiol Opt 2000;20(4):335-41.
23. Hewitt AW, Kearns LS et al. PAX6 mutations may be associated with high myopia. Ophthalmic Genet 2007;28(3):179-82.

24. Jurkus JM. Contact lenses for children. Optom Clin 1996;5(2):91-104.
25. Harnois C, Boisjoly HM, Jotterand V. Sporadicaniridia and Wilms' tumor: visual function evaluation of three cases. Graefes Arch Clin Exp Ophthalmol 1989;227(3):244-7.
26. Pinello L. Ipovisione in eta pediatrica: management clinico riabilitativo. Atti del 41° Simposio di strabologia, oftalmologia pediatrica, neuroftalmologia e ipovisione, Bolzano 12-13 ottobre 2007 (pp 25-8).
27. Legge 138/2001. Gazzetta Ufficiale 21/04/01 n. 93.
28. Decreto Ministeriale del Ministero della sanità del 27/08/99 n. 332. Regolamento recante norme per le prestazioni di assistenza protesica erogabili nell'ambito del Servizio sanitario nazionale: modalità di erogazione e tariffe. Supplemento ordinario alla Gazzetta Ufficiale 27/09/99 n. 227.
29. Legge 104/92. Gazzetta Ufficiale 17/02/92 n. 39.

Scholastic integration of children with anidridia

Luisa Pinello

Questions and recommendations

Question 16. What are the appropriate interventions to assist the scholastic integration of children with aniridia?

Current legislation

Scholastic integration refers to the active participation of children as an integral part of school education. The aim is to enable them to develop their full potential in learning and in communication, relational and social skills.

Every country has its own legislation regulating the school education of children with impaired vision. Though Italian legislation is innovative in concept, [1-7] its application has shown criticalities, [8] particularly as concerns the availability of home readers, which is more consistent in the northern areas of the country. Current legislation promotes scholastic integration and sustains the right to education of persons with low vision at all school levels. Legal provisions ensure the provision of school assistance, the development of an integrated educational plan, the assessment of deficits and difficulties, limitations, capacities, resources and actions required to attain the educational objectives appropriate for the individual child, with the involvement of professionals who must collaborate in periodic review of the integrated educational plan.

Law 104/1992 [2] provides for insertion of the handicapped at all levels of education, from crèche to university. Article 12 states, “Handicapped infants (age 0-3 years) are ensured insertion in crèches” (paragraph 1) and “The handicapped are ensured the right to education in elementary school, the regular classes of all schools of any level, and in the university” (paragraph 2).

Legislation protects persons with aniridia, who often present visual impairments and low vision, [9-13] in the school environment through the identification of services, organizational solutions and appropriate support, including:

- Advanced technologies for attaining the highest possible level of independence
- Transcription of texts into Braille, large-print letters, magnifying devices, text-to-speech systems, Braille displays, and assistive programs among others.

The law also provides for a variety of other aids for scholastic integration. Functional diagnosis is established by a panel of specialists who work with the local health district authority in collaboration with school and community services to draw up an integrated educational plan.

Teacher assistants, or aids, work under a teacher’s supervision to give students additional attention and instruction. They are assigned to students with a sensory handicap, [1,2,14] as documented by the community neuropsychiatric services; documentation will include a functional diagnosis and a dynamic functional profile that describe the child’s learning difficulties and recovery potential, which will inform the integrated educational plan.

A home reader or instructor in information technology is provided by the provincial health and social services either directly or through the Italian Union of the Blind and Partially Sighted [Unione italiana ciechi e ipovedenti (UICI)] where regulations or arrangements have been stipulated, upon request by the child’s family, with presentation of documentation/certification of vision impairment by an eye doctor. [8]

The inclusion of citizens with handicaps in the social fabric constitutes a milestone for organizations working with the disabled.

The rehabilitation centers for low vision [3] and the patient associations for the blind and partially sighted operate a variety of services for assisting in scholastic integration and providing support to the family. Most scholastic integration services are operated by the provincial offices of the UICI through collaboration with the institutions, the promotion and implementation of initiative and

agreements to overcome the barriers persons with low vision encounter at school, and providing didactic material specifically aimed at encouraging integration.

Interventions and professionals working in scholastic integration

The scholastic integration of children with visual impairments comprises specific actions based on ophthalmologic, psychological and blind pedagogy indications specific to children with aniridia, with a view to support the child's educational achievement in the perspective of his/her insertion as an active citizen in society. [15,19]

The ophthalmologist provides the school and educational agencies with a learning pathway of the child with low vision, specifying the strategies, methodologies, materials and aids most appropriate for learning activities. [12, 15,20-22] This will include regular meetings with educators to measure the child's progress, direct observation, and where required and possible, meetings with operators and community specialists to obtain a more detailed overview of the situation. As part of a multidisciplinary team, the ophthalmologist can provide opportunities for training, consultation, and additional aids, [15-17,19] cooperating with the blind teachers, the educators and the teacher assistants to evaluate the prerequisites for reading texts or reading and writing Braille, and for planning strategies to develop safe mobility and orientation outdoors. In particular, highly recommended for educational purposes are:

- Solar filters to reduce photophobia, glare and harmful UV radiation
- Optical magnifying systems for near vision in children with extremely low vision due to foveal or macular hypoplasia
- Optical magnifying systems for distance vision
- Video magnifier (fixed and portable CCTV systems) at home and at school
- Environmental modifications for adequate lighting to prevent anomalous reflection of light
- Audio books, tactile markers
- Special integrative activities in Braille reading and writing
- Computers with adaptive devices (keyboard, magnifying software, screen reader, text-to-speech software)
- Glare control
- Large-print with minimum letter height 14 points

The use of a Braille reading and writing system is highly recommended when, despite the use of magnifiers, near visual acuity requires so high an order of magnification that prolonged independent reading is not possible and text comprehension is limited. In such cases, the ophthalmologist will need to persuade the child's parents that the use of Braille does not imply that the child is totally blind.

The request for a home reader for school assistance is highly recommended. This can be done through the UICI provincial offices, presenting certification by the ophthalmologist that documents the child's visual impairment starting from elementary school. In the classroom, account should be taken of the child's reduced distance vision: the child should sit in the front row; the classroom should be fitted with a blackboard that provides strong contrast without abnormal reflection, shaded windows, and indirect lighting. [12,22,25,26]

The following school supplies are recommended to assist low vision:

- Notebooks with large-print lines
- Fine-medium-large markers or large-tipped pencils
- Books with large print and enlarged images and well-spaced lines (supplied by specialized centers in letter heights appropriate for the child)
- Large-print photocopies
- Magic markers
- Sheet paper which does not produce abnormal reflection and with strongly contrasting letters (printed black on white)

Because children with aniridia and low vision often develop fatigue and accommodation spasms or blurry vision, frequent rest periods are recommended, as are ergonomic devices that improve posture altered by anomalous head positioning to compensate for nystagmus and the absence of stereopsis due to low vision. Rational modification of the classroom, exploitation of contrasts, and adequate illumination can help the child with low vision move independently and safely at home and at school.
Also recommended are continuing education and training courses for teachers, teacher assistants and readers, with particular attention to the transfer of specific techniques and methodologies, [27] so as to avoid delegating to the teacher assistant the full responsibility for education and learning. The training of teacher assistants and readers in methodological-didactic procedures, techniques and special materials is key to promoting learning processes in children with aniridia and low vision. [8]
The role of the teacher assistant is defined in a circular issued by the Ministry of Public Education [28] as a professional with specific skills that facilitate scholastic integration.

Support, information and education for parents and indication on the choice of school education
Most parents are deeply shocked when they are told that their child has been diagnosed with a visual impairment; therefore, they need to be adequately informed about the ways in which he/she can be properly educated to ensure learning and development. [12,27,29]
Parents will require support starting from their being informed of the diagnosis [12,29] through to the scholastic choices they plan for the child. [8] The objective of the interventions recommended for scholastic integration is to promote the use of remaining vision, the use of assistive/adaptive devices, and environmental modifications to facilitate the child's development. The rehabilitation approach to supporting school integration and improving the child's quality of life will influence: [16,25]

- Learning
- Communication
- Activities of daily living
- Acquisition of safe mobility and orientation skills outdoors
- Insertion and participation in school life
- Development and emotional-relational well-being

A law [3] defines the provisions for the prevention of blindness and vision rehabilitation, social and workplace integration of the multidisabled blind or partially sighted, mandating the regional administrations to create specialized centers for these purposes.
The ophthalmologist must provide recommendations for vision rehabilitation and prescribe aids as an integral part of patient care and indications for possible rehabilitation strategies to be implemented in the school in children with aniridia and a marked loss of vision or low vision. [31,32]
While a generalized scheme of preferences and practices in school integration may respond to the needs of the majority of children with aniridia, it cannot cover all circumstances. This means that a plan that facilitates scholastic integration must be multidisciplinary and personalized to the individual child who will have different needs that require specific responses that take into account the particular circumstances of the child with aniridia and low vision.

Recommendations

GCP

A plan should be developed that promotes the scholastic integration of children with vision impairments and aniridia. The plan should be informed by the indications of a multidisciplinary, multiprofessional team that comprises an ophthalmologist, a teacher for the blind, a psychologist, educators, a teacher assistant and a reader.

GCP The multidisciplinary, multiprofessional team should provide information to the child's parents about vision impairment associated with aniridia so that they can collaborate in planning their child's learning pathway. The parents should receive information and support starting from communication of the diagnosis through to decisions about their child's education.

GCP Educators (teachers, teacher assistants, readers) should receive training and continuing education about didactic and methodologic procedures, techniques, and special materials.

GCP School assistance at home provided by a reader should be started when the child is in elementary school.

References

1. Legge 517/77. Insegnante di sostegno. Gazzetta Ufficiale 18/08/77 n. 224 (art. 2,7).
2. Legge 104/92. Legge quadro per l'assisenza, integrazione sociale e i diritti delle persone handicappate. Gazzetta Ufficiale 17/02/92 n. 39 (art.12-16).
3. Legge 284/97. Disposizioni per la prevenzione della cecità e per la riabilitazione visiva e l'integrazione sociale e lavorativa dei ciechi pluriminorati. Gazzetta Ufficiale 04/09/97 n. 206.
4. Legge 4/2004. Accesso dei disabili agli strumenti informatici. Gazzetta Ufficiale 17/01/04 n. 13.
5. Ordinanza Ministeriale 80/95. Norme per lo svolgimento degli scrutini e degli esami nelle scuole statali e non statali di istruzione elementare, media e secondaria superiore (Anno scolastico 1994/1995).
6. Ordinanza Ministeriale 330/97. Norme per lo svolgimento degli scrutini ed esami nelle scuole statali e non statali d'istruzione elementare, media e secondaria superiore. Anno scolastico 1996/9 (art. 3,4,8).
7. Ordinanza Ministeriale 128/99. Esami scolastici (art. 4).
8. Tioli E. Forme di riabilitazione ed educazione dei ciechi in Italia. Oftalmologia sociale 2006;4:19-22.
9. Harnois C, Boisjoly HM, Jotterand V. Sporadic aniridia and Wilms' tumor: visual function evaluation of three cases. Graefes Arch Clin Exp Ophthalmol 1989;227(3):244-7.
10. Lee H, Meyers K et al. Complications and visual prognosis in children with aniridia. J Pediatr Ophthalmol Strabismus 2010;47(4):205-10.
11. Pinello L, Mazzarolo M et al. Aniridia congenita: follow-up clinico ed esiti funzionali visivi. Abstract book 25° Congresso nazionale Società italiana di oftalmologia pediatrica, Ostuni, 12-14 giugno 2008.
12. Taylor D. Paediatric ophthalmology (3rd edition). Blackwell Science, London, 2005 (pp 57-76; 126-31; 244-65; 1098-102).
13. Valenzuela A, Cline RA. Ocular and nonocular findings in patients with aniridia. Can J Ophthalmol 2004;39(6):632-8.
14. Bisante E, Cordedda A. Il diritto all'integrazione scolastica dell'alunno con disabilita visiva. Oftalmologia Sociale 2008;4;34-40.
15. Castagni N. Handicap e computer. Per l'inserimento dei disabili nella scuola di tutti. Franco Angeli, Milano, 1998.
16. Colenbrander A, Fletcher D. Ipovisione e riabilitazione visiva. Verduci Editore, Roma, 1994.
17. Corn AL, Koenig AJ. Foundations of low vision: clinical and functional perspectives. AFB Press Editor, New York, 1996.
18. Corn AL. Living and learning with low vision. Proceeding Eurosight 2002 Low vision conference, Stresa, 9-10 marzo 2002.
19. Gatto F. Aspetti psicopedagogici e didattici della minorazione visiva. In: Tiflologia per l'integrazione (3/1997). Unione Italiana Ciechi, Roma, 1997.
20. Limoli PG, D'Amato L et al. Il corpo stampa quale standard internazionale per la valutazione della funzionalità visiva. In Argomenti di ipovisione. Fabiano Gruppo Editoriale, Canelli, 2000 (pp 163-71).
21. Rosenblum YZ, Zak PP et al. Spectral filters in low-vision correction. Ophthalmic

Physiol Opt 2000;20(4):335-41.
22. Zingirian M, Gandolfo E. Ipovisione. Nuove frontiere dell'oftalmologia. Fabiano Gruppo Editoriale, Canelli, 2002.
23. Pinello L. Ipovisione in eta pediatrica: management clinico riabilitativo. Atti del 41° Simposio di strabologia, oftalmologia pediatrica, neuroftalmologia e ipovisione, Bolzano 12-13 ottobre 2007 (pp 25-8).
24. Jurkus JM. Contact lenses for children. Optom Clin 1996;5(2):91-104.
25. Hyvärinen L. Considerations in evaluation and treatment of the child with low vision. Am J Occup Ther 1995;49(9):891-7.
26. McMullan R. Environmental science in building (4th edition). Palgrave Macmillan, 1998.
27. Lennon J, Harper R et al. Usefulness of postassessment reports in a paediatric low vision clinic: a questionnaire survey of parents and education professionals. Ophthalmic Physiol Opt 2008;28(3):247-52.
28. Circolare del Ministero della Pubblica istruzione del 28/07/79 n. 199. Forme particolari di sostegno a favore degli alunni portatori di handicap.
29. Rahi JS, Manaras I et al. Health services experiences of parents of recently diagnosed visually impaired children. Br J Ophthalmol 2005; 89(2):213-8.
30. Decreto Ministeriale del Ministero della sanità del 27/08/99 n. 332. Regolamento recante norme per le prestazioni di assistenza protesica erogabili nell'ambito del Servizio sanitario nazionale: modalità di erogazione e tariffe. Supplemento ordinario alla Gazzetta Ufficiale 27/09/99 n. 227.
31. World Health Organization. International classification of impairments, disabilities and handicaps. WHO, Geneve, 1980.
32. World Health Organization.Management of low vision in children, Bangkok, 23-24 July 1992(Publication 93.27). WHO, Geneve, 1993

Diseases associated with aniridia, with particular reference to cancer

Alessandro Jenkner

Questions and recommendations

Question 17. Which diagnostic examinations are recommended and how often should they be performed to detect Wilms tumor (nephroblastoma) as early as possible in patients with WAGR syndrome?

Aniridia [1] may arise as an isolated ocular malformation (hereditary disorder with autosomal dominant transmission in 70% of cases and sporadic in 30%) [2] without other associated disorders or it may occur as part of the WAGR syndrome (Wilms tumor, aniridia, genitourinary malformations, and mental retardation).[3]

The isolated form is caused by a mutation or deletion in the PAX6 gene, whereas the syndromic form is caused by a wider deletion on chromosome 11p13 involving the PAX6 gene and the neighboring WT1 gene. About 40-70% of patients with a joint deletion of the two genes will develop Wilms tumor (WT), also known as nephroblastoma, during the first years of life, whereas those with sporadic aniridia (i.e., with a PAX6 mutation but a normal WT1) do not carry this risk. [4,5] The risk is higher, however, in children with submicroscopic deletions of WT1. [6]

WT, an embryonic kidney neoplasm, is the most common renal tumor in children [7] (7% of all childhood cancers), with an incidence of 8.2 in 1 million children under the age of 15 years. Most cases of WT present with unilateral solitary lesions; about 12% develop a unilateral multifocal tumor, and about 7% bilateral renal involvement. [8] The median age at diagnosis is 42-47 months in unilateral WT and 30-33 months in bilateral WT. [9] In children with WAGR syndrome, the age at onset is even earlier (median, 22 months) with a higher incidence (17%) of bilateral tumor. [10] Though rarely, WT in WAGR syndrome may also arise later. [11] A model of development of WT suggests its origin in a genetic mutation that predisposes to the development of nephrogenic rests, abnormally retained benign clusters of embryonic kidney precursor cells with the potential for malignant transformation into WT. [12]

Detection of congenital anomalies predisposing to the development of neoplastic disease forms the basis for genetic screening programs. [13] For more than a decade, clinical surveillance and diagnostic testing for WT has been carried out in patients with aniridia, though evidence for the efficacy and risk/benefit ratio of such programs is lacking. [14]

The literature reports three retrospective studies on surveillance for WT in at-risk patients, only one of which found a difference in the stage distribution between the screened population and that with clinically diagnosed disease in Beckwith-Wiedemann syndrome: [15] 3/15 of patients resulted false positive on subsequent radiographic examination and surgery. The second study analyzed the case series of three consecutive studies within the U.S. National Wilms Tumor Study (NWTS) (involving a total of 3675 patients) and reported a slight advantage for the screened population (higher number of stage I) of patients with aniridia. [16]

An analysis of all patients registered with the U.K. National Children Cancer Registry between 1971 and 1992 (total, 1622 patients) found no difference in the stage distribution or survival between non-screened patients and those found positive or negative at screening. [17]

A recent review of the literature concluded that there is no convincing evidence that screening reduces WT-related mortality in at-risk patients and that it is unlikely in the near future that prospective studies on surveillance efficacy can be carried out. Instead, it was suggested that an empirical approach [18] should be taken, with regular testing for cancer that:

- is offered only to persons with diseases associated with a risk of at least 5% of developing WT, as in WAGR syndrome
- is initiated after genetic counseling has been obtained

- comprises kidney ultrasound examination every 3-4 months, starting from the diagnosis of the at-risk disease
- must continue up to age 5 years
- can be performed at a non-specialist center but by an ultrasonographer experien ced in pediatric sonography
- must refer suspected cases to a center specialized in pediatric oncology.

Lifelong monitoring of kidney function is fundamental: chronic renal failure develops at a young age in 38% of children with WAGR syndrome [19] and in over 90% of those with bilateral kidney tumor.[20] Such patients should also be followed-up by specialists in the associated extrarenal disorders.

The approach to children with clinical suspicion of WT includes confirmation by diagnostic imaging studies. Abdominal ultrasound is the procedure of choice as it permits optimal visualization of the abdominal cavity. Further details of a renal mass documented on ultrasound scans can be obtained with contrast-enhanced abdominal computerized tomography (CT) or magnetic resonance imaging (MRI). MRI can distinguish WT from nephrogenic rests, however, the final diagnosis rests on histological examination. [21] Positron-emission tomography (PET) is not part of initial diagnostic work-up for WT though the tumors will usually be detected on PET scans. [22]

The differential diagnosis includes other primary renal neoplasms, which are no more common among patients with syndromic WT than in the general population. Non-neoplastic diseases that can be mistaken for WT include nephrogenic rests, polycystic kidney disease, hydronephrosis, abscesses, and renal bleeding.

Neuroblastoma, an embryonic tumor of the adrenal gland, may be clinically and radiographically confused with nephroblastoma but can be differentiated by the distinguishing feature of elevated urinary catecholamine concentrations.

Recommendation

IV/B Screening for WT in children with WAGR syndrome should include clinical examination and renal ultrasound every 3 months after a diagnosis of aniridia and thereafter up to 5 years of age.

Question 18. What is the recommended treatment for WT in children with WAGR syndrome?

Nephroblastoma is the paradigm of success in the multidisciplinary treatment of childhood cancer. Indeed, the survival rate is about 90% in patients with localized disease and 70% in those with metastatic disease. [21,23-25]

The approaches to diagnosis and therapy are well-established (based on the work of international cooperative groups), though the protocols of the Children's Oncology Group (COG) differ substantially from those of the Société Internationale d'Oncologie Pédiatrique (SIOP). Because staging is performed at different time points (at disease onset or after neoadjuvant chemotherapy), the protocols are not directly comparable. Staging may be broadly defined as follows: tumor restricted to the kidney and completely excised (stage I); tumor extending beyond the kidney but completely excised (stage II); incomplete excision with macro- or microscopic residual disease, tumor rupture, regional lymph node involvement or neoplastic thrombus (stage III); hematogenous metastases (lung, liver, bone, brain) or distant lymph node metastases (stage IV); bilateral renal tumor (stage V).

Surgery and chemotherapy play a centrally important role in the treatment of WT, whereas radiotherapy is reserved for selected cases. [26-28]

Since nephroblastoma can metastasize to the lungs, chest radiography and/or CT should be part of initial work-up for WT, though the prognostic significance of micrometastases seen on CT scans but not detectable with conventional radiography remains to be elucidated. [29-31]

Surgery entails nephrectomy, which is usually performed at onset of the disease (COG protocol) or after 4 weeks of cytoreductive chemotherapy (SIOP protocol). Nephron-sparing surgery (tumorectomy or heminephrectomy) is indicated in bilateral disease. [32,33] Because of the risk of (metachronous) occurrence of WT in the contralateral kidney in patients with WAGR syndrome, the SIOP (SIOP2001) and the Italian Association of Pediatric Oncology (AIEOP-TW 2003) protocols both recommend partial nephrectomy – when technically feasible – over radical nephrectomy in patients with unilateral syndromic WT and not only bilateral synchronous tumor. [34] Since preoperative chemotherapy for bilateral disease reduces tumor volume and seems to enhance the possibility of conserving a greater volume of functioning renal parenchymal tissue, preoperative chemotherapy should precede surgery (conservative when possible) in patients with WAGR syndrome. Owing to difficulties with therapy management and conservative surgery, patients with WT in WAGR syndrome should be referred to centers with extensive experience in the medical and surgical treatment of renal neoplasia in children.
Chemotherapy entails the administration of vincristine and actinomycin for histologically favorable WT stages I and II (absence of anaplasia and blastema after preoperative chemotherapy), with the addition of doxorubicin in histologically favorable WT stages III and IV. Radiotherapy is reserved for stage III (delivered to the side or the abdomen depending on the extension of intraabdominal neoplasia) and for stage IV delivered to the lung fields if complete remission of lung metastases has not been obtained after the first chemotherapy cycle (6-9 weeks) or if metastases are present in sites other than the lungs, which is rare in WT. Treatment of histologically unfavorable WT (anaplasia or persistence of blastema after preoperative chemotherapy) includes vincristine, actinomycin, doxorubicin, cyclophosphamide, etoposide, and carboplatin. Therapy for histologically favorable WT is usually performed in the out-patient setting, whereas therapy for at-risk forms is more intensive and is delivered in the in-patient setting.
Following nephrectomy, patients with advanced disease (stages III and IV) receive radiotherapy to the tumor bed and to lung metastases in some cases.
Nephroblastoma arising in WAGR syndrome presents certain peculiar characteristics: younger age at onset; higher incidence of bilateral disease; frequent presence of intralobar nephrogenic rests; and an invariably favorable histology[10]. Children with WAGR syndrome respond well to treatment and have a 5-year survival rate after WT diagnosis comparable to that of patients with nonsyndromic WT. Life expectancy worsens with the development of chronic kidney failure at a young age in 38% of patients; [19] 90% of those with WAGR and bilateral tumor will eventually develop chronic kidney failure[20]. The estimated survival rate of patients with WAGR syndrome at 27 years after the diagnosis of nephroblastoma is 48% or less, as compared to the 86% survival rate in those with sporadic WT. [10,19,20] About 5-10% of those with nephroblastoma have bilateral or multifocal disease. The prevalence of bilateral disease is higher in patients with genetic forms, [10] and 85% of those with WAGR syndrome will develop a unilateral WT. [35]

Recommendations

I/A WT in WAGR syndrome should be treated according to currently available national or international protocols for WT.
Patients with WT in WAGR syndrome should be referred to and followed-up at centers with extensive experience in the medical and surgical management of WT in children.

References

1. Hingorani M, Moore A. Aniridia. In: Pagon RA, Bird TD et al (eds). GeneReviews [Internet]. University of Washington, Seattle, 1993- (updated 12-08-2008).
2. Netland PA, Scott ML et al. Ocular and systemic findings in a survey of Aniridia subjects. JAAPOS 2011;15:562-6.
3. Fischbach BV, Trout KL et al. WAGR syndrome: a clinical review of 54 cases. Pediatrics 2005;116:984-8.
4. Gronskov K, Olsen JH et al. Population-based risk estimates of Wilms tumor in sporadic aniridia. A comprehensive mutation screening procedure of PAX6 identifies 80% of mutations in aniridia. Hum Genet 2001;109:11-8.
5. Muto R, Yamamori S et al. Prediction by FISH analysis of the occurrence of Wilms tumor in aniridia patients. Am J Med Genet 2002;108: 285-9.
6. van Heyningen V, Hoovers JM et al. Raised risk of Wilms tumour in patients with aniridia and submicroscopic WT1 deletion. J Med Genet 2007;44:787-90.
7. Miller RW, Young JLJ, Novakovic B. Childhood cancer. Cancer 1995;75:395-405.
8. Pastore G, Znaor A et al. Malignant renal tumours incidence and survival in European children (1978-1997): report from the AutomatedChildhood Cancer Information System project. Eu J of Cancer 2006;42:2103-14.
9. Breslow N, Olshan A et al. Epidemiology of Wilms tumor. Med Pediatr Oncol 1993;21:172-81.
10. Breslow NE, Norris R et al. Characteristics and outcomes of children with the Wilms tumor aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol 2003;21:4579-85.
11. Royer-Pokora B, Beier M et al. Twenty-four new cases of WT1 germline mutations and review of the literature: genotype/phenotype correlations for Wilms tumor development. Am J Med Genet 2004;127A:249-57.
12. Dome JS, Coppes MJ. Recent advances in Wilms tumor genetics. Curr Opin Pediatr 2002; 14:5-11.
13. Clericuzio CL. Recognition and management of childhood cancer syndromes: a systems approach. Am J Med Genet 1999:89:81-90.
14. Beckwith JB. Children at increased risk for Wilms tumor: monitoring issues. J Pediatr 1998; 132:377-9.
15. Choyke PL, Siegel MJ et al. Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. Med Pediatr Oncol 1999;32:196-200.
16. Green DM, Breslow NE et al. Screening of children with hemihypertrophy, aniridia and Beckwith-Wiedemann syndrome in patients with Wilms tumor: a report from the National Wilms Tumor Study. Med Pediatr Oncol 1993; 21:188-92.
17. Craft AW, Parker L et al. Screening for Wilms tumour in patients with aniridia, Beckwith syndrome or hemihypertrophy. Med Pediatr Oncol 1995;24:231-4.
18. Scott RH, Walker L et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child 2006;91:995-9.
19. Breslow NE, Takashima JR et al. Renal failure in the Denys-Drash and Wilms' tumor-aniridia syndromes. Cancer Res 2000; 60:4030-2.
20. Breslow NE, Collins AJ et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 2005;174: 1972-5.
21. Dome JS, Huff V. Wilms tumor overview. In: Pagon RA, Bird TD et al (eds). GeneReviews [Internet]. University of Washington, Seattle, 1993. (19-12-2003; aggiornato il 14-06-2011).
22. Moinul Hossain AK, Shulkin BL et al. FDG positron emission tomography/computed tomography studies of Wilms' tumor. Eur J Nucl Med Mol Imaging 2010;37:1300-8.
23. Pritchard-Jones K. Controversies and advances in the management of Wilms tumour. Arch Dis Child 2002;87:241-4.
24. Spreafico F, Bellani FF. Wilms' tumor: past, present and (possibly) future. Expert Rev Anticancer Ther 2006;6:249-58.
25. Jenkner A, Diomedi Camassei F et al. 111

renal neoplasms of childhood: a clinicopathologic study. J Pediatr Surg 2001;36:1522-7.
26. Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist 2005;10:815-26.
27. Wu HY, Snyder HM, D'Angio GJ. Wilms' tumor management. Curr Opin Urol 2005;15:273-6.
28. Nakamura L, Ritchey M. Current management of Wilms' tumor. Curr Urol Rep 2010; 11:58-65.
29. Meisel JA, Guthrie KA et al. Significance and management of computed tomography detected pulmonary nodules: a report from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys 1999;44:579-85.
30. Grundy PE, Green DM et al. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group. Pediatr Blood Cancer 2012;59:631-5.
31. Smets AM, van Tinteren H et al. The contribution of chest CT-scan at diagnosis in children with unilateral Wilms' tumour. Results of the SIOP 2001 study. Eur J Cancer 2012;48:1060-5.
32. Ritchey ML. Renal sparing surgery for Wilms tumor. J Urol 2005;174:1172-3.
33. Ritchey ML. Nephron sparing surgery for Wilms tumor. Where is the future? J Urol 2011; 186:1179-80.
34. Indolfi P, Jenkner A et al. Synchronous bilateral Wilms tumor: A report from the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). Cancer 2013 Jan 10. doi: 10.1002/cncr. 27897 (in pubblicazione).
35. Huff V. Wilms tumor genetics. Am J Med Genet 1998;79:260-7.

The information and assistance procedures for patients and their families

Barbara Poli, Corrado Teofili

Questions and recommendations for information

Question 19. What is the content of the information, and how does the manner and timing of its communication to those people affected by aniridia and their families facilitate informed choices as to their assistance?

The timing of the communication of the diagnosis is a crucial step in the life of a family affected by any rare disease. Factors such as how the information is communicated, the attention to the accuracy and the comprehensibility of the information provided, the willingness not to leave parents alone with the diagnosis is understood to significantly affect the impact of the diagnosis on the family. It is also important that professionals who assist the patient do not take for granted any of the phases in the exchange of information, so that the parents immediately adopt a conscious competent approach in the difficult challenge that they face.

A checklist may be useful in order to structure the discussion and to ensure that the professionals offer all the basic information. An example of a checklist may be found in Appendix 2.

Recommendations

GCP Parents should be directed to the regional centres that deal with children with visual impairment, so that, in the early months of the child's life, the parents can receive assistance and be taught techniques to encourage the development of the patient's oculomotor coordination and his/her visual functions.

GCP Specific attention must be given to reinforce the skills of the parents of children with aniridia by providing them with adequate information and training. It is important to make available, where necessary, also psychological support, so as to facilitate the sharing and implementation of options regarding treatment, rehabilitation and welfare; and to facilitate the proper establishment of the parent-child relationship.

GCP Information should be given to the adult patient or family of the child on the current legislation that regulates the national network of rare diseases and the procedures to apply for exemption from the correlated expenses in relation to using health services (Decree 279 /2001). In particular, it is also recommended to specify that aniridia is a rare disease in this Annex 1 of Decree 279/2001 (with code RN0110) for the provision of benefits under the exemption. For this purpose, the specialist of the health unit must provide a diagnosis certificate with which the Local Health Authority can issue an exemption certificate.

GCP It is recommended to provide information relating to the disability certificate and the economic aid available for children with visual impairment and for their parents, indicating to the family which health districts and other institutions are involved, so as to facilitate access to care and support.

GCP Families should be given information on the existence of the association dedicated to aniridia (Aniridia Italiana) that brings patients with this disease and their families together, as well as on the existence of other associations of patients who have visual impairment or who have rare diseases.

Questions and recommendations for types of care

Question 20. Which organisational aspects should be considered in the planning of care to patients with aniridia and their families?

At the moment of birth, every newborn has a check up that, among other things, also has to diagnose any malformations[1]. It is important to detect the existence of any eye diseases early in order to ensure, in addition to appropriate treatment, the effectiveness of rehabilitative interventions[2].

The EurordisCare3[3] research - as far as aniridia is concerned it was conducted in 6 European countries (Cyprus, Denmark, France, Italy, Norway and Spain) - noted that the average age of diagnosis was 2 years old. Often the recognition of anomalies that lead to diagnosis (for example, the presence of nystagmus) was made by parents and/or by a paediatrician during the first and second months of life, in other cases the delay in diagnosis extended to several months and sometimes went beyond one year.

Even if there are well-established procedures in place in Italian hospitals for the early detection of abnormalities/malformations, there is still significant room for improvement in the time of diagnosis of aniridia with important consequences on the implementation of early rehabilitation procedures aimed at encouraging the development of visual function in children in the first months and years of life.

Equally for aniridia, as with all rare diseases, the multidisciplinary approach is necessitated by the complexity of pathology. The professional figures that may be involved in the diagnosis, treatment, rehabilitation and support of a patient with aniridia are: the geneticist, the practitioner and the paediatrician, a specialist in an ophthalmology centre of expertise that expresses an opinion on the patient's condition and possible actions to be executed, the specialist in ophthalmology centre to which reference is made for periodic check ups. To these are added the professional child psychiatrist who oversees the neurological development of the child, the psychologist, the specialist in typhlology, the school doctor, the special needs teacher, the normal class teacher, the educational assistant and the social worker.

As for the patient, regardless of his/her age, it is therefore of fundamental importance to define the modalities of effective coordination between the various actors involved in the diagnosis, treatment and management of disease.

It is also important to emphasise that the concept of care should include both the strictly clinical as well as the social aids[4].

Recommendations

GCP

In order to improve the quality of the clinical care and to minimize the delay in diagnosis, it is recommended to refer the patient with suspected aniridia to clinical centres (in accordance with Decree 279 /2001) in which only professionals that have attained the most clinical experience in this condition work, and which are equipped with diagnostic imaging and molecular-genetic facilities (hospitals, university departments, IRCSS), where you can embark on an appropriate diagnostic path and apply specific treatment protocols. If this is not possible, it is recommended to build and promote a dedicated service network that is capable of ensuring all the phases of diagnostic and care.

GCP In order to ensure an appropriate and timely diagnosis of aniridia, so as to identify any associated malformation syndromes and appropriate diagnostic and follow-up, it is recommended that in the professional training of neonatologists, paediatricians, paediatric oncologists, child psychiatrists, psychologists, gynaecologists, general practitioners and community services the information is included in a systematic way so as to improve knowledge in the field of rare diseases, including those concerning the eye, and to favour in clinical practice the formulation of the suspected diagnosis of the rare eye condition and appropriate clinical management of the patient also at a local level .

GCP It is recommended, from the time of diagnosis of aniridia in an infant, that there is collaboration between the specialist eye doctor who made the diagnosis and the paediatrician of the young patient, so as to provide information about the disease and what the follow-up results are. It is also recommended that this cooperation will continue later, so that the paediatrician is informed on the evolution of the disease and the specialist ophthalmologist is available to respond to any clinical questions that may arise during the development of the child. It is recommended that the same approach also be adopted by the specialist ophthalmologist and general practitioner who assist the adult.

GCP Hospital should favour the smooth implementation of the protocols of surveillance and monitoring visits, by assisting the family with their planning and taking all necessary organisational measures (for example, the concentration of multiple visits on the same day), minimising obligations and simplifying the procedures for access to care .

GCP It is recommended that among the professionals involved in assisting the patient with aniridia there should be direct coordination to ensure the better management of the disease that includes the personal and social life of the patient. In some cases, depending on the complexity of the clinical manifestations and the impact of the diagnosis on the family unit, it may be useful to have someone in the role as a coordinator, such as the case manager at the local health district where the patient is resident.

GCP If surgery needs to be performed in a hospital and/or by a specialist different from who usually follows the patient, it is recommended that the two specialists remain in contact and work together to ensure the careful and successful management of postoperative and follow–up phases in the medium and long term. In particular, a common approach should be agreed upon to assess the patient's clinical condition and the performance of instrumental analysis to minimise the travelling of affected individuals.

GCP To permit the monitoring of the disease and the planning of health interventions, as well as to promote research, it is recommended that the patient’s data collected by the respective clinical centres identified within the national network for rare diseases, are transmitted to the Regional Registry of Rare Diseases and then to the National Register at the National Centre for Rare Diseases of the Institute of Health .
It is also recommended to provide adequate information to patients and family members about the purpose of the register.

References

1 . Presidential Decree of the Council of Ministers of 9 July 1999. Policy and coordination of the Regions and Autonomous Provinces of Trento and Bolzano regarding investigations helpful to the early diagnosis of malformations. Gazzetta Ufficiale No. 170, of 22 July 1999.

2 . Ministry of Health. Appropriateness in the prevention, diagnosis and therapy in ophthalmology.
Notes of the Ministry of Health 2011; 11:4. Available at: http://www.quadernidellasalute.it/archivio-quaderni/11-settembre-ottobre-2011.php (visited on 15/01/2013) .

3. Eurordis. The voice of 12.000 patients: experiences and expectations of rare diseases patients on diagnosis and care in Europe. A report based on the EurordisCare2 and Eurordiscare3 surveys. Eurordis, 2009 (p 101). See: http://www.eurordis.org/IMG/pdf/-voice_12000_patients/EURORDISCARE_ FULLBOOKr.pdf (visilted 15-01-2013).

4. Eurordis. Position paper on Centres of expertise and European reference networks for rare diseases.
Eurordis, 2008 (pp 3-4). See: http://www.eurordis.org/IMG/pdf/position-paper-EURORDIS-centres-excellencenetworksFeb08.pdf (visited 15-01-2013).

Appendix 1. Aids for the visually impaired

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A sensory disability such as impaired vision significantly compromises the autonomy of the affected people in different spheres and at different levels of their lives. You only have to think of personal care, independence in the management of the home, the care of the family, mobility, study, play, work, hobbies, social relations and access to information for this to be apparent.
Each of these issues implies solving the numerous problems and barriers they present and as such requires the use of aids and customisable technology.
In order to provide some general guidance, this section lists some of the most frequently used aids available. It should be noted that the choice of aid should always be made carefully by assessing the capabilities, needs, expectations, as well as the physical and psychological characteristics of the person who will use them.

Optic assistive devices for near and far vision

Magnifying glasses
The use of magnifying glasses enhances the autonomy of people with aniridia, making it easy to read through the use of portable tools. It should be taken into consideration that while using a lens the field of vision is reduced, and that the larger the degree of magnification the more the field of vision is reduced as is also the available light. Therefore the magnification factor should always be determined as low as possible, compatible with the visual capability of the person, so as to get the most range and obtain the most light on what you read.
The key features of magnifiers are:

- field of vision
- degree of magnification
- variability of the magnification factor
- additional light
- dimensions
- ergonomic characteristics.

Monoculars and binoculars
Since these are small in size they are more portable. Some monoculars, besides ensuring long distance vision (for example, reading a street sign or a house number), allow close vision (about 20-30 cm) and are therefore useful, for example, for reading message boards, intercoms, etc.
The key features of monoculars and binoculars are:

- field of vision
- magnification factor
- flexibility of the focus
- size of the instrument
- quality of the lens.

With the use of this type of aid the visual field is very limited, as the magnification factor is very high, and this creates problems because of the reduction of the overall view. This can be troublesome for the persons who use it, as they have to get used to "finding" what they want to see and, sometimes, in a limited time.
One must also consider that it takes time before a person can exploit the potential of this tool.
It is important to make the appropriate choice of the degree of magnification so as to have it as small as possible, in order to attain the widest possible field of vision.

Electronic assistive devices (hardware and software)

There are many software and hardware products that cater for special needs and that promote personal autonomy. For example video magnifiers, software to process music, to scan and recognise texts, large print and/or Braille printers, tools for printing graphics in relief, mobile phones, media players, digital recorders, satellite receivers, specific tools for the writing/reading newspapers and books, and for research services, educational software for mathematics and other subjects. Below we outline a few, remembering that any choice must be made after an assessment of the capacity and needs of the person concerned.

Video magnifiers

These are divided into 3 basic categories: fixed, portable and pocket (electronic lenses). In addition to enlargement, they permit the use of different levels of contrast and brightness and have a degree of magnification greater than that of a simple lens. They can also be used for seeing things at a distance (for example, reading a blackboard, signs outdoors, an intercom, etc.)
The key features of fixed video magnifiers are:

- degree of magnification
- autofocus
- fixed or variable focus
- brightness
- different levels of contrast and colours
- colour or black and white
- flexibility of the camera
- the screen is usually interchangeable
- possibility of integration with a computer.

Portable and pocket video magnifiers have the same characteristics as fixed, but are not restricted to the location and therefore are useful in many other contexts.
Additional features compared to the fixed are:

- size of the screen
- still image
- image memory
- image processing
- ergonomic features
- dimensions of the device.

Computer aids

Any personal computer can be personalised directly through its operating system, so as to improve its use and in some cases make it usable without the need of any aids.
As for individuals who need more specific support the distinction between visual impairment and blindness can be decisive in the choice of aids.
In people without sight or with a negligible residual vision, you can use different screen readers, specifically, software that intercepts all that a sighted person sees on a screen. This software can be connected with either a speech synthesizer or with a Braille display and allows access to, and use of personalised computer at various levels.
For the visually impaired, there is other magnification software, which can be integrated with a speech synthesizer. This software, as well as enlarging what is written on the screen provides support for other visual difficulties encountered by a visually impaired person. These include allowing the contrast and the combination of colours to be adjusted, providing various kinds of pointers, affording different levels of magnification, brightness etc.

In case there is also the built-in voice synthesizer, it should be noted that, in addition to the common features, it also affords specific features catering for the visually impaired.

There are valuable tools available on the market that, while not having been developed as aids for the visually impaired and the blind, deserve to be mentioned because they offer concrete support for the performance of many activities. They may have a vocal, tactile (Braille) and/or enlarged print output, and input via touch screen, keyboard and voice.

Smartphones and **tablets** can be considered as personal computers, and their portability makes them, in fact, indispensable aids to mobility.
They allow the installation of applications for the performance of many activities of daily living, such as the acquisition and reading of short texts on paper, reading newspapers, decoding of barcodes, consulting package leaflets of medicinal products, planning and the management of routes, timetables, journey times and stops of public transport, orientation and mobility, the magnification of objects and environments, recording (including memos), translation, writing texts.

In addition to the numerous applications that they support, these tools also allow access to the web, which further extends the range of accessible information in mobility. Communication is also an important aspect (telephone calls, sending text messages, e-mail, chat, participation in conferences).

The distinguishing features of these devices are the ease and immediacy of use, which surely also favour the adoption by individuals less accustomed to using personal computers.
The parameters to consider in the selection of a device of this type are:

- size of the display, which encourage greater visibility to the visually impaired
- portability, as it ensures the use of mobility, very important to support those who have a limited ability to access information
- accessibility, i.e., the possibility of independent access to the various functions, thanks to the assistive settings that the visually impaired can adopt
- usability, which refers to the ability of the person and the ease of use of the device .

Electronic book readers (**eBook readers**) are portable devices designed for reading texts in digital format. They allow access to multimedia content that also extends the method of reading by the visually impaired. The display can be personalised and in some cases they are equipped with text-to -speech (TTS) which allows you to listen to books through a human-sounding voice that reads the text.

Appendix 2. Checklist of information to patients

General information	What is aniridia Type and frequency of examinations Epidemiology Prognosis Genetics
Pediatric patients	Evaluation of visual function Development of motor and praxis skills, neuropsychological, cognitive, affective-relational, and language-communication abilities Visual rehabilitation Correction of refraction defects Support for parents School integration
Daily living	Photophobia Low vision Artificial tears Personal independence Orientation and mobility Eyeglasses and contact lenses Assistive/adaptive devices Work Free time Sports
Psychological and social issues	Certifications, exemptions, entitlements Sensory barriers Disability Discrimination Self esteem and self image
Support organizations	Reference to organizations dealing with the specific disorder, vision impairments, and rare diseases

Appendix 3. List of acronyms

BCVA: Best Corrected Visual Acuity
BUT: Break-up Time Test
ERG: Electroretinography
FISH: Fluorescent In Situ hybridization
HRT: Heidelberg Retinal Tomography
IOL: Intraocular Lens
MLPA: Multiplex Ligation-dependent Probe Amplification
NWTS: National Wilms Tumor Study
OCR-ICR: Optical Character Recognition-Intelligence Character Recognition
OCT: Optical Coherence Tomography
OMIM: Online Mendelian Inheritance in Man
PET: Positron Emission Tomography
EVP: Evoked Visual Potentials
MRI: Magnetic Resonance Imaging
SOX: Sry-related HMG box
TTS: Text-To-Speach
UBM: Ultrasound Biomicroscopy