The Ocular Communique

The Journal of the Maharashtra Ophthalmological Society

Editor : Dr. B. K. Nayak

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Instructions to Authors

The Journal of Maharashtra Ophthalmological Society publishes three issues in a year. It accepts original articles, rare case reports and short reviews. All the articles are subject to editorial revision.

1. All the papers should be accompanied by a statement that, they have not been published in any other journal or presented in any conference and that, if accepted they will not be offered to any other publisher / conference without the consent of the Editorial Board. All the authors should sign in this statement.

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4. The title along with the author's name, address of the institution, and reprint request must be typed in a separate page.

5. The manuscript in the case of scientific papers must be in the following format:

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Editorial Office :
Dr. B. K. Nayak
P.D. Hinduja National
Hospital, Veer Savarkar
Marg, Mahim, Mumbai - 16.
Tel.: 24447127, 24447176
Fax: 91-22-24440425
Mbl.: 9987315599
E-mail:
drbknayak@gmail.com

Editorial

Dear Colleagues,

Greetings from the Editor's Office of JOMOS.

Publication in scientific journals, brings instant recognition and extreme joy to the authors. At the same time, it serves a much bigger cause of advancement of science. The MCI guidelines for promotion of teachers and professors make it mandatory to have certain number of publication to their credit. Hence, everyone must publish.

It has been said by Sir James Bailey, Editor of the Academy of Management Learning and Education, that "The man of science appears to be the only person who has something to say just now, and the only man who does not know how to say it". This statement has two parts, the first part represents the completion of research which logically leads to second part i.e scientific writing. As a general principle scientific writing should be short, clear and substantive. Scientific writing should follow the woodford model according to which "clear writing is the writing that cannot be misunderstood".

Publication in high impact factor peer reviewed journal is the ultimate goal but writing articles for JOMOS could be a good starting point. I invite all the members for contribution to JOMOS. To brush up the art and skills of scientific writing Indian Journal of Ophthalmology in association with P D Hinduja National Hospital & Medical Research Centre, Mumbai conducts regular courses. Please take advantage of this initiative.

Regards,

DR. BARUN KUMARNAYAK
EDITOR – IN – CHIEF
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Indigenous methods of visual acuity testing in pre-school children

Dr. Parikshit Gogate, Dr.Vandana Chakane , Prof. Madan Deshpande

Summary

Early recognization of subnormal vision in children would prevent amblyopia, but visual acuity measurement in pre-school children requires specialized charts. Their cost makes them unaffordable to most primary eye clinics. Our study aimed to use indigenously available substances to measure the form visual acuity in pre-school children.

The visual acuity was measured using Indian sugary sweets (cost $0.09) -'Battasa' (white crunchy sugar discs), murmure (roasted puffed rice grains) and paracetamol (acetaminophen) tablets and validated against Cambridge (for 2-5 year old children, $488) and Cardiff (for <2 year old children, $1025) charts. 110 eyes of 55 children had their visual acuity tested by both the methods. Upto two years of age, identifying the Battasa roughly correspond to 20/400, while the tablet corresponds to 20/200. In the 2-6 years age, identifying the tablet and murmure corresponds to 20/200 visual acuity. Mothers, ophthalmic assistants and anganwadi workers could be trained for their use.

Key words:

Visual acuity, pre-school children, refractive errors.

Uncorrected refractive errors and amblyopia are a major cause of severe visual impartment in children.[1,2] Early detection of these disorders would go a long way to ameliorate them as delay in their recognition leads to amblyopia.[3] Visual acuity measurement in pre-school children requires specialized visual acuity testing charts.[4,5] But the cost of these charts ($1000 and more) makes them unaffordable to most primary eye clinics and schools where this examination needs to be conducted. If a cheaper, easily available alternative method of pediatric vision assessment is found, more children could be easily examined at an earlier age and their vision quantified sooner and their blindness and/or visual impairment (especially unilateral) discovered. Our study aimed to use indigenously available substances to measure the form visual acuity in pre-school children.

Materials and Methods

The study was conducted at the Orbis supported pediatric ophthalmology department of a comprehensive eye care centre in 2005-6. The visual acuity of pre-school children was measured using locally made Indian sweets -'*Battasa*' (white crunchy sugar discs- used in most Indian festivals and easily and cheaply available in most parts of the country), *murmure* (roasted puffed rice grains) and paracetamol (acetaminophen) tablets and validated against Cambridge (for 25-60 month old children) and Cardiff (for 6-24 month old children) charts. The Cambridge card was based on the principle that the letters subtend on angle of 5 minutes at nodal point with individual stroke of the letter subtending an angle of one minute (cost Rs.20 177; $ 488). The visual acuity was estimated at a distance of three meters for each eye at a time. The child was handed over a card with HOTVX and is asked to match the letters on the chart. For the Cardiff cards, the preferential looking of child towards the picture at one meter was noted as positive response (cost Rs.46120; $1025). The study was approved by the ethical committee of the hospital.

For the indigenous method, we used Murmure, Battase and paracetamol tablets stuck on a black card sheet (cost Rs.5; $0.09). This was done to have a white on black contrast. The card sheet was held at 3 meters distance and child was asked to identify the object. The mother would report if the child identified the object or not. The child was not asked to name the object, assuming that some children of that age may not be able to name it verbally. The answer of each child was recorded on their terms (e.g.: The 'battasa' would commonly be called a moon, coin or a ball, similarly for the tablet) in visual acuity column. The results were then compared with standard visual acuity chart. Statistical analysis was done using STATA and the Pearson's chi square test.

Result

One hundred and ten eyes of 55 children had their visual acuity tested by both the novel and the formal methods. Thirty-five out of 55 (65%) were male. Sixteen children (32 eyes, 29%) were<24 months of age. Of the 55 children, 30 had normal vision, while 16 had refractive errors, four were with congenital cataracts, three were pseudophakic, one had corneal opacity and one was with a limbal dermoid.

In age group of 6-24 months, of those whose vision was perception of light (PL) - <20/400, no one could identify a tablet and murmure, but 33% (eyes) could identify 'battasa's (shown in table1).

Of those whose visual acuity was 20/200-20/80, almost 75% identified 'battasa' and tablets. This meant that if a child <2 yrs of age couldn't identify 'tablet' at a distance of 3 meter, his visual acuity was < 20/400 (severe visual impairment by WHO standard), and such a child should be referred to an ophthalmologist for further evaluation. Battasa could be a cut-off for 20/400 visual acuity.

In age group of 25-60 months, of those with PL -20/400 visual acuity, 71% could identify 'battasa', 57% a tablet and 14% 'murmure' (shown in table 2).

Table 2 shows the comparison of visual acuity by

Dr. Parikshit Gogate
H.V. Desai Eye Hospital, Pune, India.

indigenous methods with Cambridge cards in 25-60 month's age group. If child of this age group can't identify murmure or tablet at 3 meter, his visual acuity is probably <20/200.

Discussion

Up to two years of age, the most crucial period of visual development, identifying the Battasa roughly correspond to 20/400 (3/60, blind by WHO standards), while the tablet fairly corresponds to 20/200 (6/60, the WHO standard for severe visual impairment). Such children need a referral to a pediatric ophthalmology clinic for further examination. If the children can identify murmure their parents can be safely told that their child has near normal vision. In the 2-6 years age group, identifying the tablet and murmure corresponds to 20/200 visual acuity.

Mothers, ophthalmic assistants, 'dais' – traditional birth attendants, health workers, and anganwadi workers (Integrated Child Development Scheme workers who work for mother and pre-school child care under a Government of India program) could be trained for use of these indigenous methods of visual acuity measurement. Battasa, murmure and tablets could be substituted by other locally available things, which are familiar to children. But these need to be validated with standard visual acuity testing charts. They are not intended to replace the traditional pediatric vision testing charts, but can be a useful substitute where none are available. Even if the child eats or handles them, it should not be a cause for concern. Ophthalmologists and optometrists should be sensitized to their need and importance; so they can be supportive, and not dismissive about such methods. The limitations of the study are its small sample size. For a particular visual acuity level, if child of 5 year was able to identify an object, a child of same vision <2 yrs of age may not able to identify the same. The size of the sweets used may vary, they are also three dimensional objects pasted on a sheet of black paper and were thus not standardized.

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Table 1: Comparison of visual acuity by Cardiff cards and indigenous method in 6-24 month's age group.

Cardiff acuity		PL-<3/60	3/60-<6/60	6/60-6/24	≥6/18
Battasa dia 32 mm	Identified	1 (33%)	2 (67%)	3 (75%)	17 (78%)
	Not identified	2 (67%)	1 (33%)	1(25%)	5 (22%)
Tablet dia 9 mm	Identified	0	0	3 (75%)	16(73%)
	Not identified	3 (100%)	3 (100%)	1 (25%)	6 (27%)
Murmure 12*4 mm	Identified	0	0	0	9 (41%)
	Not identified	3 (100%)	3 (100%)	4 (100%)	13 (59%)
Number of eyes		3 (100%)	3 (100%)	4 (100%)	22 (100%)

Using STATA and by Pearson chi2 (2) = 13.0510, Pr = 0.001 with aggregate data.

Table 2: Visual acuity with Cambridge cards compared with indigenous methods for age group of 25-60 months (78 eyes)

Cambridge acuity		PL-<3/60	3/60-<6/60	6/60-6/24	≥6/18
Battasa dia 32 mm	Identified	5 (71%)	6 (66%)	9 (90%)	49 (94%)
	Not identified	2 (29%)	3 (34%)	1 (10%)	3 (6%)
Tablet dia 9 mm	Identified	4 (57%)	3 (34%)	8 (80%)	43 (83%)
	Not identified	3 (43%)	6 (66%)	2 (20%)	9 (17%)
Murmure 12*4 mm	Identified	1 (14%)	2 (22%)	7 (70%)	41(79%)
	Not identified	6 (86%)	7 (78%)	3 (30%)	11 (21%)
Number of eyes		7 (100%)	9 (100%)	10 (100%)	52 (100%)

Using STATA and by Pearson chi2 (2) = 11.59, Pr = 0.003 with aggregate data.

Pharmacological considerations in cataract surgery

Dr. Sarvesh Tiwari, Dr. B. K. Nayak,

Cataract surgery is one of the most commonly performed operations in the world. Postoperative infectious endophthalmitis is the most feared and devastating complication of cataract surgery. Although advances in surgical techniques and instrumentation during the last 20 years have reduced its incidence, postoperative infectious endophthalmitis following phacoemulsification continues to occur at a frequency of 0.1% or less. [1] Because this pathologic condition is rare, its relative infrequency has made it difficult to design and conduct randomized, controlled trials that will produce uniform guidelines for cataract surgeons to abide by in order to further minimize the complication. In the absence of evidence-based guidelines, surgeons derive treatment algorithms and practices from empirical observations and theoretical analysis to reduce the risk of the infection in patients. Interestingly, although the role of prophylactic antibiotics in "clean cases" continues to be debated in other surgical specialties, there is virtual unanimity among cataract surgeons in advocating antibiotic prophylaxis following uncomplicated cataract surgery. More accurately, the debate in the ophthalmic community has focused on the timing and delivery of prophylaxis-pre-, intra- and/or postoperatively, via drops or intracameral instillation.

Though cataract surgery, has nowadays, become a day care procedure, the pre and perioperative period require certain pharmacological considerations.

This can be further classified into

- Modification of existing medications if any
- Medication for prophylaxis
- Drugs in special situations

Modification of existing medication

For patients on Anticoagulant therapy

It is a common practice to advice stoppage of antiplatelet drugs or anticoagulant therapy prior to cataract surgery in order to minimize the risk of intraoperative bleed. Stopping anticoagulants can cause fatal emboli, but sight-threatening bleeds may occur if anticoagulation is continued. The surgeon is thus subjected to the therapeutic dilemma which may have fateful consequences!

Effects of anticoagulants on ophthalmic surgery were studied and it was proposed that Anticoagulation had no effect on the number of significant perioperative (choroidal) haemorrhages. Aspirin had little effect on bleeding during vitreoretinal surgery. Warfarin, however, was associated with bleeding complications. It was suggested that aspirin should not be stopped prior to surgery. Warfarin may be stopped if the patient's thromboembolic risk is low.[2]

For patients on Glaucoma therapy

The primary concern about Prostaglandin deravatives in these patients is the possible association between their use and cystoid macular edema (CME) following surgery It has been recommended, stopping prostaglandins 1 week prior to surgery in high-risk patients when their IOP can be controlled by other agents such as oral carbonic anhydrase inhibitors (CAIs) or when their glaucoma is not severe enough to place them at significant risk of ultimate visual deterioration. The 1-week preoperative stopping date is completely arbitrary, as it remains unknown how long the adverse effects (if any) of prostaglandins last, following the drugs' discontinuation.[3,4]

For patients on Treatment for BHP(Benign Hypertrophy of prostrate :Tamsulosin)

FDA and Boehringer Ingelheim are warning prescribers of cases of intraoperative floppy iris syndrome (IFIS) during cataract surgery(phacoemulsification) in men treated with alpha1-blockers including Tamsulosin.

Prior to cataract surgery, healthcare providers should ask male patients specifically whether they have been treated with tamsulosin or other alpha1-blockers. In men who have received these agents, surgical risks were reduced by using a variety of alternative small pupil management strategies like using iris hooks, iris dilator rings, or viscoelastic devices Discontinuing tamsulosin prior to cataract surgery did not reduce the severity of IFIS in this prospective trial. Surprisingly, IFIS can occur up to several years after discontinuation of tamsulosin. [5-7]

Medication for Prophylaxis

One of the most feared complications of this surgery is endophthalmitis that, although infrequent, leads to high visual morbidity even with appropriate treatment. For this reason, ophthalmologists adopt several measures for its prophylaxis.[8]

1. Prevention of infection
   Preoperative Antibiotics
   Preoperative antiseptics
2. Prevention of perioperative miosis
3. Prevention of CME later

Infection source

- Micro-org directly introduced from environment
- Haematogenous spread of organisms as a metastatic infection
- Common predisposing factors are

Dr Sarvesh Tiwari
P. D. Hinduja National Hospital, Mahim, Mumbai

immunocompromised status, septicemia or IV drug abuse
- Iatrogenic via contaminated surgical instruments irrigating fluids etc.

Most common potential source of infection is the periocular flora of the patient 75% of conjunctival cultures from normal eyes harbour *S. epidermidis, S. aureus* and various *streptococci* Similar pattern has been found in eyes with post-operative endophthalmitis Role of external ocular bacterial flora in the pathogenesis of post-op endophthalmitis has been proven by DNA studies[9]

Administration of Antibiotics

Bacteria are the most common group of causative agents of endophthalmitis and gram-positive pathogens are responsible for 60 to 80% of acute infections. [7] Previous studies have shown that most bacteria responsible for postoperative ocular infection are part of the normal microbiota of the conjunctiva and eyelids of the patient.[10-11] The culture is positive in 50 to 85% of the vitreous aspirates and the *coagulasenegative Staphylococcus (Staphylococcus epidermidis)* is the most frequently isolated pathogen, followed by *S. aureus* and *Streptococcus spp*, gram-negative organisms are responsible for 20% of the infections.[12] It is known that the use of prophylactic antibiotics in cataract surgery reduces the number of organisms in the conjunctiva and eyelids,[8-9] other desirable characteristics are good bioavailability, broad-spectrum coverage and favorable susceptibility patterns[10-12]

Scottish intercollegiate guidelines Network (SIGN) guidelines for prophylaxis
- Reduce the incidence of SSI (Surgical Site Infection)
- Supported by evidence
- Normal bacterial flora should not be disturbed
- Minimal adverse effects
- Minimal effect on patients host defences

Role of prophylactic antibiotics

Antibiotic prophylaxis in cataract surgery is highly recommended to prevent ocular complications.[13] Studies have shown that prophylactic antibiotic reduces the number of conjunctival bacteria at the time of surgery

Optimal choice of pre-operative topical antibiotic depends on
- Spectrum of bacteria covered
- Rapidity of killing
- Duration of action
- Penetration and toxicity of antibiotic
- Antibiotic susceptibility pattern
- Cost of antibiotic

Administration of antibiotics

Preoperative and perioperative antibiotics can be administered in the following ways
1. Topical
2. Systemic
3. Oral
4. Parenteral

Topical fluoroquinolones (Fqs) are commonly used prophylactic agents because of their broad spectrum of activity covering the majority of these pathogens found in endophthalmitis including indole positive and gram negative organisms. Third generation FQs (Ciprofloxacin, Ofloxacin): widely used as prophylactic agents nowadays.

The question remains that what is the ideal time for starting prophylactic antibiotics? Several studies have been conducted regarding this.

A study comparing 3 days vs 1 hr pre-op use of FQs as prophylactic antibiotic was conducted.[14]

Aim: To determine the efficacy of reducing conjunctival bacterial flora with topical FQs (Ofloxacin) when given for 3 days compared to 1 hour before surgery.

Methods

89 patients (92 eyes)

Study group (44 eyes)

1 drop q.i.d for three days + 1 drop every 5 mins, 1 hour prior to surgery

Control group (48 eyes)

1 drop every 5 mins, 1 hour prior to surgery

All patients: a scrub of 5% povidone iodine for a minute + 2 drops of 5% povidone iodine

Conjunctival cultures obtained and inoculated

Description of time points when cultures were taken

Time pointsDescription
- 5 days pre-op before topical antibiotic
- Before topical ofloxacin on the day of surgery
- After 1 hr pre-op antibiotic, before scrub
- After povidone iodine scrub, immediately before surgery
- Conclusion of surgical procedure

Result

The application of topical FQ for 3 days before surgery appears to be more effective in eliminating bacteria from conjunctiva than application 1 hour before surgery.

Another study conducted by some authors proved that The application of topical 0.5% levofloxacin for 1 or 3 days significantly reduced the number of eyes with positive conjunctival cultures. The addition of 5% povidone-iodine further eliminated bacteria from the conjunctiva. The application of levofloxacin for 1 day appears to be as effective as a 3-day application [15]

However in recent times a disturbing trend regarding resistance to FQs is being observed. A number of recent studies have reported emerging resistance to FQs among ocular isolates particularly among gram positive organisms. In recent years, up to 30% or more of *S. aureus* strains are found to be FQ resistant.

To tackle this problem recently fourth generation FQs have emerged, and are being rapidly used for antibiotic prophylaxis prior to cataract surgery. The fourth generation FQs like gatifloxacin, moxifloxacin have enhanced activity against gram positive pathogens.Organisms resistant to earlier gen FQs are susceptible to fourth gen FQs. Secondly they are less prone to encourage development of resistant strains [16]

Aim : To study in vitro potency of 2nd, 3rd, 4th generation fq's for: bacterial endophthalmitis is olates.

The Median MICs (µg/ml) of 93 Bacterial Endophthalmitis Isolates to Ciprofloxacin (CIP), Ofloxacin (OFX), Levofloxacin (LEV), Gatifloxacin (GAT), and Moxifloxacin (MOX) (17)

Organism	N	CIP	OFX	LEV	GAT	MOX	Potency by rank (p=0.05)
Resistant SA	8	64	64	12	3.5	1.75	mox>gat>lev>cip=ofx
Susceptible SA	6	.32	.63	.22	.11	.06	mox>gat>lev=cip>ofx
CoagNeg Staphylococcus FQR	10	64	64	38	2.0	2.5	mox = gat > lev = cip = ofx
CoagNeg Staphylococcus FQS	10	.13	.38	.13	.09	.05	mox > gat > cip = lev > ofx
Streptococcus pneumoniae	10	.75	2.0	.63	.22	.09	mox > gat > lev = cip > ofx
Steptococcus viridans	10	.97	2.0	.75	.25	.13	mox > gat > lev = cip > ofx
Beta-hem Streptococcus	5	.5	1.5	.75	.25	.13	mox > gat > cip = lev > ofx
Enterococci species	9	.75	2	.75	.38	.19	mox > gat > lev = cip > ofx
Bacillus species	9	.13	.38	.13	.09	.09	mox = gat > lev = cip > ofx
Gram negatives	16	.06	.19	.08	.06	.08	cip = gat = lev = mox > ofx

Source: A J Ophth Volume 133, Issue 4, Pages 463-466 (April 2002)

FQR = Resistant to ciprofloxacin and ofloxacin as determined by disk diffusion;

FQS = Susceptible to ciprofloxacin and ofloxacin as determined by disk diffusion; ">" = indicates significantly greater potency; "=" = indicates equal potency;

Resistant SA = Staphylococcus aureus resistant to ciprofloxacin and ofloxacin as determined by disk diffusion;

Susceptible SA = Staphylococcus aureus susceptible to ciprofloxacin and ofloxacin as determined by disk diffusion.

In vitro study suggests that the 4th generation FQ are more potent than the 2nd and 3rd generation FQ for gram-positives and equally as potent for gram-negatives. The 4th gen FQ appear to cover 2nd and 3rd generation FQ resistance. In animal models gatifloxacin was proven to have superior ocular penetration than ciprofloxacin. Another animal study has shown gatifloxacin to have equivalent ocular penetration to Ofloxacin.

In a study to evaluate the penetration of gatifloxacin ophthalmic solution 0.3% into human aqueous humor of Patients undergoing cataract surgery it was found that The mean aqueous humor concentration of gatifloxacin achieved in this study meets or exceeds MIC (minimal inhibitory concentration) values against commonly found bacterial ocular pathogens, including species of Staphylococcus and Streptococcus. The mean concentration (± SD) of gatifloxacin in aqueous humor was 1.26 ± 0.55 mcg / mL.

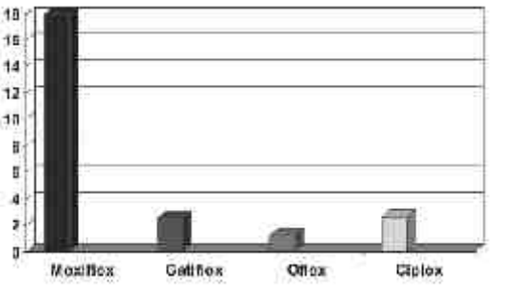
Role of Systemic Antibiotic Prophylaxis

The role of systemic antibiotics in prevention and treatment of endophthalmitis remains debatable. There is a belief that intraocular inflammation and / or performance of vitrectomy may alter the blood retinal barrier in a manner to allow better penetration of systemic administered antibiotics. Of all Antibiotics FQs have been found to have excellent ocular penetrability. They are lipid soluble bactericidal and are copiously secreted in tears. However there are certain reservations against the use of prophylactic systemic antibiotics are

1. Systemic toxicity
2. Variable intravitreal penetration
3. High cost of antibiotics
4. Development of resistant strains.

In a study to asses the vitreous and aqueous penetration of orally administered moxifloxacin in humans. It was found that moxifloxacin has a spectrum of coverage that encompasses the most common organisms in endophthalmitis. The pharmacokinetic findings of this investigation reveal that orally administered moxifloxacin achieves therapeutic levels in the noninflamed eye. Because of their broad spectrum of coverage, low MIC against 90% levels, good tolerability, and excellent oral bioavailability, fourth-generation FQs may represent a major advance for managing posterior segment infections.[18-20]

Topical Fluoroquinolone concentration in human conjunctival tissue (20)



A number of different sources have been implicated as origins of possible infection in ocular surgery. Some of these include the eyelids, eyelashes, conjunctiva, and nasal secretions. One study demonstrated that organisms isolated from the vitreous were genetically indistinguishable from those recovered from the eyelids, conjunctiva, or nose in 14 of 17 cases of endophthalmitis[21] Gram-positive organisms are part of the normal flora of the skin, nares, and conjunctiva, and interestingly the Endophthalmitis Vitrectomy Study demonstrated that 94% of isolates recovered from eyes with postoperative endophthalmitis had gram-positive organisms, 70% of which were due to coagulase-negative staphylococci.[22] Various methods of prophylaxis have been attempted, including preoperative lash trimming, irrigation with saline solution, topical antibiotics, irrigating solutions containing antibiotics, postoperative subconjunctival antibiotic injection, and postoperative collagen shields presoaked in antibiotics. [23-26] The goal of all these interventions is to decrease the incidence of postoperative endophthalmitis. In an evidence-based update, it was found that only preoperative povidone-iodine preparation received an intermediate clinical recommendation, indicating that povidone-iodine use is only moderately important to clinical outcome.[26] Nonetheless, povidone-iodine is currently the "gold standard" of preoperative ocular surface sterilization. Just prior to surgery ,the skin of the eyelids is prepared by scrubbing it with 10% Povidone iodine while the conjunctiva is prepared by instilling 5% povidone iodine drops in the conjunctival fornices.

Vancomycin in Irrigating fluid

Recent interest in the advocation of vancomycin in the irrigating fluid during cataract surgery to reduce chances of postoperative endophthalmitis is being reviewed.However a study conducted proved that the use of supplemental prophylactic vancomycin in the irrigating solution during extracapsular lens extraction is associated with increased incidence of cystoid macular edema [27]

Intracameral antibiotics

If the purpose of antibiotic prophylaxis is to clear an inoculation of organisms introduced during surgery, then the antibiotic should be in the anterior chamber at the time of introduction or shortly thereafter.[28] The intracameral administration of antibiotics provides the greatest intraocular bioavailability. Given the findings of the Endophthalmitis Vitrectomy Study, the relative frequency of gram-positive organisms, and their 100% susceptibility to vancomycin, the drug is an attractive and viable option for intracameral antibiotic prophylaxis.

Recently, cefuroxime has been proposed and used as an intracameral prophylactic antibiotic. According to the ESCRS study on Endophthalmitis, prophylactic ceufuroxime administered intracamerally reduced the risk of endophthalmitis to one fifth of if no prophylactic antibiotic is used. Cefuroxime is a second-generation cephalosporin that works by bacteriocidal, beta-lactam action-inhibiting penicillin-binding proteins, which prevent cross-linking of peptidoglycan strands normally needed for the cell wall's integrity and leads to osmotic lysis of the bacterium. Cefuroxime provides less gram-positive coverage than vancomycin, while providing some gram-negative coverage, notably against *Haemophilus influenzae, Escherichia coli, Klebsiella,* and *Proteus*. It has only been described for intracameral injection.

The most convincing data to support the use of vancomycin infusion come from Mendivil and Mendivil,[29] who reported a reduction in the culture-positive intraocular aspirates from 13% to 5%, 2 hours after cataract surgery. All bacteria cultured were sensitive to vancomycin. Furthermore, the investigators determined that 47% of the initial concentration of vancomycin remained in the anterior chamber, significantly greater than the approximate 0.5- to 2.0-µg/mL MIC of most bacteria that are responsible for endophthalmitis. The pharmacokinetics derived from this study were used to generate an *in vitro* model by Libre et al. [30] that simulated decreasing vancomycin levels during an 8-hour period, approximately four half-lives; demonstrating a 1,000-fold reduction in the amount of methicillin-resistant *Staphylococcus aureus* colony-forming units as compared with controls. In a retrospective study, Gimbel et al.[1] reported on almost 12,000 surgeries without a single case of postoperative infectious endophthalmitis while utilizing a gentamycin infusion and in-the-bag injection of vancomycin.

The greatest opposition to the prophylactic use of intracameral vancomycin stems from concerns regarding increasing drug resistance. Vancomycin is typically used in bacterial infections that are life threatening or recalcitrant to other antimicrobial therapies. In the wake of increasing vancomycin resistance, the Centers for Disease Control and Prevention and the AAO jointly issued a statement in 1999 discouraging the use of vancomycin for surgical prophylaxis in cataract surgery.

Critics have pointed out that an intraocular dose of 1mg, distributed over 40L of body water, is equivalent

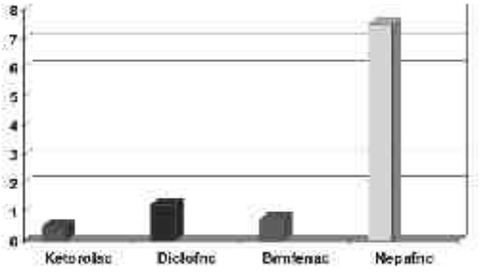
to a systemic dosage of 0.025µg / mL, which is much too low to affect an exposed organism's survival and reproduction. Thus, a 1-mg dose of vancomycin creates no pressure on an organism to develop resistance.[28]

Goals of NSAID prophylaxis

Nonsteroidal antiinflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, edema ,pain etc are reduced. They primarily act by

- Inhibition CME following cataract surgery [31]
- Prevention of intraoperative miosis during cataract surgery [32]
- Reduction of pain and discomfort following cataract surgery [33]
- Management of postoperative inflammation [33]

In a study to To evaluate the aqueous humor concentrations and cyclooxygenase (COX) inhibitory activities of various NSAID like nepafenac, amfenac, ketorolac, and bromfenac after topical ocular administration of nepafenac 0.1%, ketorolac 0.4%, or bromfenac 0.09%. in eyes; it was found that nepafenac showed significantly greater ocular bioavailability and amfenac demonstrated greater potency at COX-2 inhibition than ketorolac or bromfenac.



Uveitis

In patients with a history of long standing Uveitis many authors have advised perioperative antiinflammatory therapy in the form of 1mg / kg / day oral Prednisolone unless contraindicated along with topical steroids and topical as well as oral NSAI started two days prior to surgery.

These are continued for at least a week after surgery and then tapered. Such therapy is usually not necessary in milder forms of inflammation such as Fuch's Heterochromic Uveitis, but all cases which have required oral immunosuppression in the form of steroids or other agents to control their uveitis in the past should preferably be given such a regime.

Special care is to be taken in patients with long standing renal diseases like diabetic nephropathy or chronic renal failure as regards to pre and post cataract surgery chemoprophylaxis.The primary antibiotics linked to acute renal failure in humans like aminoglycosides, beta lactams (cephalosporins, penicillins, penems), rifampicin, vancomycin, sulfonamides, fluoroquinolones, and tetracylines. Aminoglycosides and beta lactams should be administered with care to avoid precipitating acute renal toxicity.

In summary cataract surgery though being a relatively safe day care procedure , does require a thourogh pre and post surgery chemotherapy management to ensure faster wound healing with better patient comfort and safety.

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Nonsteroidal Anti-inflammatory Drugs in Ophthalmology

Dr.Sarika Ramugade, Dr. B. K. Nayak

Introduction

Corticosteroids used to be the mainstay of topical therapy in the management of ocular inflammations [1], but their anti-inflammatory effect was outweighed by serious adverse effects like elevation of intraocular pressure, progression of cataracts, increased risk of infection and worsening of stromal melting [2].Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medications worldwide. NSAIDs are increasingly employed in ophthalmology to reduce miosis and inflammation ,manage scleritis ,and prevent and treat Cystoid macular oedema (CME) associated with cataract surgery and in the control of pain after photo refractive keratectomy [3]. NSAIDs have also been found to be useful in decreasing bacterial colonization of contact lenses and prevent bacterial adhesion to human corneal epithelial cells [4].In recent years ,the U.S.Food and Drug Administration has approved new topical NSAIDs,and previously approved NSAIDs have been reformulated.[5,6,7] The present article mainly gives an insight into topical ocular delivery of NSAIDs.

Commercial preparations of NSAIDs

NSAIDs are a chemically heterogenous group of compounds that inhibit the formation of eicosanoids and lack a steroid nucleus, and are biosynthetically derived from cholesterol [6].

There are six major classes:

1) Salicylates : Aspirin
2) Indole acetic acid derivatives: Indomethacin, Bendazac
3) Aryl acetic acid derivatives: Diclofenac, Ketorolac, Nepafenac, Bromfenac, Tolmetin
4) Aryl propionic acid derivatives:Ibuprofen, Flurbiprofen, Ketoprofen, Naproxen, Oxaprozin, Pranoprofen, Suprofen
5) Enolic acid derivatives: Piroxicam,Meloxicam
6) Fenamates: Meclofenamate ,Mefenamic acid

COX-2 specific NSAIDs : Celecoxib

The topical formulations of NSAIDs are limited to the relatively water soluble classes : indole acetic, aryl acetic, and aryl propionic acids. [8]

Indomethacin 1%(Merk Sharp &Dohme,Whitehouse Station ,NJ) is an indole acetic acid derivative ,currently only available outside of the united states [9]. Flurbiprofen 0.03% (Allergan ,Inc.,Irvine ,CA) is water –soluble aryl propionic acid derivative approved by the U.S. FDA for prophylaxis of surgical miosis . Flurbiprofen 0.03% is administerd 4 times ,starting 2 hours before surgery .Ketorolac tromethamine 0.5% (Allergan ,Inc) is an aryl acetic acid derivative and approved by FDA for post-cataract inflammation ,seasonal allergic conjunctivitis and to reduce post-refractive surgery discomfort. 0.4% concentration of ketorolac tromethamine reduces incidence of burning and stinging [10,11]. Diclofenac 0.1% (Novartis Ophthalmics ,Duluth,GA),also an aryl acetic acid derivative,is approved by FDA for reducing inflammation after cataract surgery and to reduce pain after refractive surgery .Ketorolac and diclofenac are dosed four times daily following cataract surgery.

Nepafenac 0.1%(Alcon laboratories) is a prodrug that is rapidly converted to amfenac after passage through the cornea is dosed 3 times daily and is the only suspension among the topical NSAIDs. Bromfenac 0.09% (ISTA Pharmaceuticals,Inc.,Irvine,CA) is dosed twice daily .These two topical NSAIDs are aryl acetic derivatives are now approved by FDA for post cataract surgery pain and inflammation .

FDA approved indications and dose [12,13,14,15]

1)Postoperative cataract extraction inflammation

a) Bromfenac (0.09%) :1 drop BID ,Starting 24 hrs after cataract surgery for 2 weeks
b) Diclofenac (0.1%): 1 drop QID ,Starting 24 hrs after surgery through 2 weeks
c) Ketorolac (0.5%) :1 drop QID ,Starting 24 hrs after cataract surgery for 2 weeks
d) Nepafenac (0.1%) :1 drop TID the day prior to surgery ,the day of surgery ,and through the first 2 weeks

2)Postoperative pain or photophobia after corneal or incisional refractive surgery

a) Diclofenac (0.1%): 1-2 drops 1 hr prior to surgery ,then 1-2 drops 15 min after surgery ,then QID for upto 3 days
b) Ketorolac (0.4%) and (0.5%) solution : 1 drop QID for upto 3-4 days after surgery

3)Inhibition of intraoperative miosis

a) Flurbiprofen (0.03%): 1 drop every ½ hr Starting 2 hrs before surgery

Pharmacokinetics

All NSAIDs are well absorbed by the GI tract and Reach a peak serum levels in 1 to 3 hours .They are metabolised by the liver and excreted in the urine and bile and are highly protein bound in plasma (typically >95%) usually to albumin .NSAIDs are weak acids

Dr. Sarika Ramugade
P. D. Hinduja National Hospital, Mahim, Mumbai

with pKa mostly between 3.5 and 4.5, and are poorly soluble in water. Aqueous ophthalmic solutions of NSAIDs have been made using sodium, potassium, tromethamine and lysine salts or complexing with cyclodextrins / solubilizer. Ocular penetration of NSAID demands an acidic ophthalmic solution where cyclodextrin could prevent precipitation of drug and minimize its ocular irritation potential.

After a single topical application ,0.03% flurbiprofen and 0.1% diclofenac reach peak aqueous cocentration of 60ng / ml and 82ng / ml at 2.0 and 2.4 hours respectively [16].The concentration of diclofenac remains above 20 ng / ml for over 4 hours and is detectable after 24 hours . Flurbiprofen is undetectable after 7.25 hours .

Nepafenac is a prodrug that is rapidly converted into the more potent NSAID amfenac by intraocular hydrolases.In vitro studies have shown a six-fold greater corneal penetration by nepafenac compared to diclofenac[17] .Bromfenac is structurally identical to amfenac with the exception of a bromine atom at the C4 position .This key alteration may increase bromfenacs penetration into ocular tissue.

Pharmacodynamics

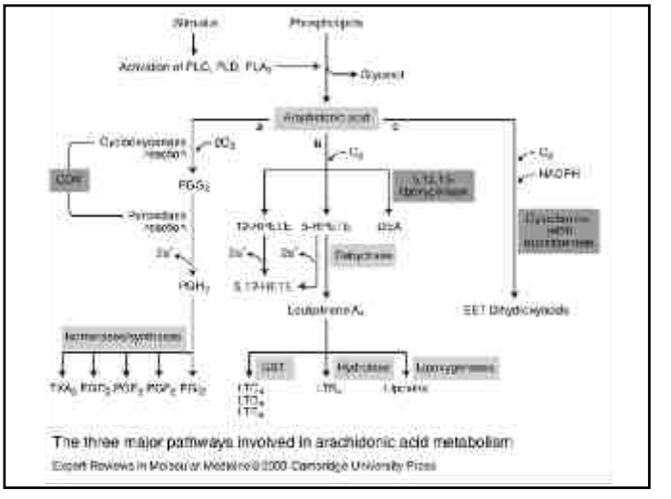
Acidic lipids are produced in the arachidonic cascade. Arachidonic acid is released from the phospholipid component of the cell membrane by the action of phospholipase A2.The arachidonic acid so produced enters either the cyclooxygenase or lipoxygenase pathway. Activation of cyclooxygenase pathway results in formation of PGs and thromboxanes, while the lipoxygenase pathway yields eicosanoids (hydroxyeicosatetraenoic acid and leukotrienes).

All NSAIDs inhibit Cyclo Oxygensnase (COX) enzymes and thereby the formation of excessive endogenous PGs including PGE2,PGD2,PGF2α,and PGI2. These endogenous PGs act on iris smooth muscle ,promote vasodilation ,disrupt the blood ocular barrier ,increase leucocyte migration ,stimulate pain,facilitate allergic responses and regulate IOP .[5,6,7,18]

Cyclooxygenase (COX) is an enzyme that is responsible for formation of important biological mediators called prostanoids including prostaglandins ,prostacyclin and thromboxane . Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain .

Two main isoforms of COX, COX-1 and COX-2, have been identified. A third isoform COX-3, remains uncharacterized .[19] COX-1, a constitutive enzyme, synthesizes PGs that regulate physiologic processes and present in most tissues. COX-2 is an inducible enzyme that is expressed throughout the body, primarily during inflammatory responses and in association with pain or fever, but may be constitutively expressed in the absence of inflammation in sites such as the brain and kidneys.[20] COX-2 is the predominant isoform in human pigment epithelium cells and is significant up-regulated in response to pro inflammatory cytokines. [21] COX-2 is present in choroidal neovascularisation and also in other highly vascularized lesions, and its expression increases in diabetic retinopathy. [22,23,24]

Ocular actions of PGs are manifested in three ways [25]. Firstly, they act on intraocular pressure (IOP). PGE1 & E2 increase the IOP by local vasodilation and increased permeability of blood aqueous barrier. On the other hand PGF2 lowers the IOP which is attributed to increased uveoscleral outflow. Secondly they act on iris smooth muscle to cause miosis. Thirdly, PGs cause vasodilation and increase the vascular permeability resulting in increased aqueous humor protein concentration.



NSAIDs do not inhibit lipooxygenase (LPO) thus they have decreased anti-inflammatory effects compared to corticosteroids ,which inhibits both LPO and COX .NSAIDs have anti-inflammatory and anti-angiogenic effects independent of their inhibition of COX .[26,6]

Ketorolac is the most potent inhibitor of COX-1 while both bromfenac and amfenac arre the most potent inhibitor of COX-2 .[8,27]Bromfenac is reported to be a 3 to 18 times more potent inhibitor of COX-2 than diclofenac ,amfenac,and ketorolac .[8,28]

USES OF NSAIDs IN OPHTHALMOLOGY

1)Prevention of surgically induced miosis

Suprofen 1% and flurbiprofen 0.03% were the first

NSAIDs approved by FDA .[5,6,7] Suprofen eye drops have been found to be useful in treatment of contact lens associated giant papillary conjunctivitis [29]. Suprofen does not interfere with the stromal wound healing [30].

2) POSTOPERATIVE INFLAMMATION

A) Cataract surgery

Several clinical studies have shown that topically applied 1% indomethacin ,0.03% flurbiprofen ,0.4% and 0.5% ketorolac ,0.1% diclofenac ,0.1% nepafenac ,and 0.09% bromfenac all decrease postoperative inflammation after cataract surgery without significant toxicity when used appropriately [17,31,32,33,34,35,36] Only four of these drugs are FDA approved for postoperative reduction of inflammation . NSAIDs are more effective at reestablishing the blood aqueous barrier as observed by flare on slit-lamp and quantitatively measured with ocular fluorophotometry[5,6,7,35,36] . Topical NSAIDs may be used in place of or in addition to topical corticosteroids after cataract surgery to avoid excessive inflammation and to improve visual recovery .

None of the studies reviewed by the FDA used topical NSAIDs more than 24 hours before cataract surgery but a well-designed studies suggest potential benefit of preoperative dosing regimens of upto 3 days.At present there is no evidence to suggest one topical NSAID treatment is better than another in controlling postoperative inflammation with the exception that flurbiprofen 0.03%appears less effective than other NSAIDs.

B) Glaucoma surgery

The effect of topical NSAIDs following glaucoma procedures in reducing the inflammation appears modest ,and thus far the FDA has not approved any of this indication .

Studies suggest that topical flurbiprofen 0.03% and diclofenac 0.1% decrease inflammation and may reduce pain following laser trabeculoplasty and to a lesser extent after cyclocryotherapy .[37,38,39]

C) Strabismus surgery

Topical diclofenac 0.1%was superior to dexamethasone 0.1% in terms of patient comfort ,conjunctival inflammation and chemosis up to 4 weeks after strabismus surgery.

Several prospective randomised studies have demonstrated that topical NSAIDs are at least comparable to corticosteroids in reducing pain and inflammation in pediatric patients after strbismus surgery. [40,41]

D) Vitreoretinal surgery

Two recent prospective,randomized,double masked ,placebo-controlled trials have demonstrated reduction of anterior chamber cell and flare after vitrectomy by 0.4% ketorolac and 0.1% diclofenac .[42,43]

3)PREVENTION AND TREATMENT OF CME

A)Pophylactic treatment of CME following cataract surgery

A large ,randomised ,double masked ,placebo –controlled trial demonstrated that 0.03% flurbiprofen and 1% indomethacin were effective at preventing CME during a 6-month period after cataract surgery, ,but the effect was not sustained [44]. Although the meta-analysis published in 1998 concluded there is benefit from prophylactic treatment of CME following cataract surgery ,[45]it remains unclear whether prophylactic treatment prevents the onset of chronic CME or in some way decrease its severity.

B)Treatment of CME following cataract surgery

CME associated with cataract surgery may be treated early (less than 6 months)or late (6 months or more)following its diagnosis .These two groups are distinguished as acute and chronic CME [46]. A more recent study reported an effect from ketorolac on macular edema noted more than 24 months following cataract surgery ,but the study was uncontrolled. There is no FDA approved therapy for the prevention and treatment of CME following cataract surgery available evidence suggests that topical NSAIDs may prevent and treat CME when used alone or concurrently with corticosteroids.

C) CME following vitreoretinal surgery

The reported incidence of CME following retinal detachment repair with scleral buckling ranges from 9%to 43% and may delay visual recovery [47,48]. Topical indomethacin may reduce the incidence of CME after scleral buckling surgery. Persistent angiographic CME may occur in up to 70% and 80%of eyes after vitrectomy surgery for epiretinal membrane (ERM) and macular hole respectively.

4) RELIEVING DISCOMFORT AND PAIN AFTER OCULAR SURGERY AND TRAUMA

Pain often occurs after radial keratotomy and excimer laser photorefractive keratectomy .Both 0.4% and 0.5%ketorolac trometamine and 0.1% diclofenac sodium are FDA approved to reduce pain and photophobia after refrractive surgery [5,6,7].In VR surgery IV ketorolac significantly reduces postoperative pain and nausea.Both diclofenac and ketorolac benefit after photocoagulation procedures .[49]

5) ALLERGIC CONJUNCTIVITIS

Topical 0.5%ketorolac is only NSAID that is FDA –approved for the treatment of seasonal allergic

rhinoconjunctivitis [50]. There is evidence that topical 0.03% flurbiprofen and systemic flurbiprofen are beneficial for signs and symptoms of hay fever.

6) UVEITIS AND OTHER INFLAMMATORY OCULAR DISEASES

A) Uveitis

At present NSAIDs are not indicated for primary treatment of anterior uveitis in view of the greater experience with and efficacy of corticosteroids and despite the fact that NSAIDs do not cause cataract or increase in IOP .

Two prospective randomised studies involving patients with acute ,non-granulomatous uveitis found higher cure rates among patients treated with 0.5% prednisolone disodium phosphate versus a non-commercially available NSAID preparation ,5%tolmetin sodium dehydrate[51,52].

B) Orbital pseudotumor

Systemic NSAIDs have been used to treat orbital inflammatory disease since the 1970s and there is one case report of orbital myositis treated with oral indomethacin[53] .

C) Episceritis and Scleritis

Episceritis doesn't require therapy,it may respond to topical medications,including NSAID.[54]

Topical NSAIDs are not effective ,systemic NSAIDs are used as first line agents ,an overall response rate of 30-92% has been reported with diffuse and nodular scleritis [55].Indomethacin at 25-50 mg three times daily is most commonly used .A recent report indicated that the COX-2 selective NSAID celecoxib at daily doses ranging from 200-800 mg was effective in controlling diffuse anterior scleritis in 92% of patients without producing any gastrointestinal side effects [56].

D) Inflamed pinguecula and pterigia

Topical indomethacin provided dramatic relief of signs and symptoms during 14 days of treatment compared to placebo [57].

E) Viral conjunctivitis

In hospitalised patients with severe measles conjunctivitis ,a randomised study compared topical 0.5% ketorolac and indomethacin 0.1% to artificial tears [58].ketorolac and indomethacin were more effective in decreasing conjunctival hyperemia.

F) Ocular inflammation in Dry Eye Patients

Topical corticosteroids and NSAIDs have been considered as an alternative to conventional tear replacement and preservation strategies in dry eye patients however Corneal perforation and melts have been reported [59].

7) RETINAL AND CHOROIDAL DISEASE

A)Diabetic retinopathy (DR)

Rheumatoid arthritis patients taking salicylates had a reduced incidence of DR [60]. This observation was examined in two clinical trials ,the one is Early Treatment Diabetic Retinopathy Study (ETDRS),this examined the effect of 650 mg of aspirin on advanced DR .Second is Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) Study ,which tested the impact of 990 mg aspirin in patients with early DR .

Although no benefit was found in patients with more advanced DR in ETDRS ,a significant effect was seen in the DAMAD study ,where higher doses of aspirin were found to slow the development of retinal microaneurysms . This later observation is supported by a recent prospective,randomised study where treatment with the NSAID sulindac prevented the develpoment and progression of DR [61].Therapeutic inhibition of COX-2 in the retina may now be achievable with topical 0.1% nepafenac and 0.09% bromfenac .

B) Age-related Macular degeneration

COX -2 is a promoter of angiogenesis and can be detected in human choroidal neovascular membrane .Inhibition of COX-2 by NSAIDs reduces VEGF production and directly inhibits CNV in both trauma –induced and ischemic-induced animal models [22,24].

C) Ocular tumors

COX-2 expression is increased in both uveal melanoma and retinoblastoma [62,63]. Experimental studies have shown that nepafenac inhibits proliferation of human retinoblastoma cell lines ,reduces progression of uveal melanoma and increases its radiosensitivity [64].

CONTRAINDICATIONS

All medications are contraindicated in patients hypersensitive to the drug itself or any of its components.

1) Bromfenac is contraindicated in ASA / NSAID induced asthma,third trimester of pregnancy
2) Ketorolac in hypersensitivity to aspirin
3) Nepafenac in hypersensitivity to other NSAIDs .

TOXICITY WITH SYSTEMIC NSAIDs

1) CNS reactions –headache,somnolence ,dizziness ,depression ,fatigue,anxiety ,confusion ,insomnia and psychotic episodes.
2) GI toxicity- nausea ,anorexia ,vomitting ,dyspepsia ,diarrhea ,constipation, peptic ulceration and bleeding .
3) Renal-acute renal failure ,salt and water retention

,hypertension ,hyperkalemia ,papillary necrosis and interstitial nephritis ,nephrotic syndrome and acute tubular necrosis .

4) Hematological toxicity
5) Hepatic toxicity
6) Dermatologic reactions
7) Metabolic changes
8) Hypersensitivity reactions [65].

TOXICITY WITH TOPICALLY APPLIED NSAIDs

1) Transient burning,stinging and conjunctival hyperemia are common
2) Allergic and hypersensitivity reactions
3) Superficial punctate keratitis ,corneal infiltrates and epithelial defects
4) Postcataract surgery atonic mydriasis [6,66].

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Duane's retraction syndrome

Dr Ramesh Murthy

Introduction

Duane's retraction syndrome (DRS) is a rare, congenital disorder which occurs in approximately 1 in 50 patients with strabismus [1]. It was first reported by Hueck in 1879 after which several variations have been described. [2] Historically never claimed, but Duane's retraction syndrome is one clinical entity which is named after Alexander Duane. It has been known to exist for more than a century now and there have been several attempts to explain the cause of the mis-wiring and the complex eye movements seen in DRS. The purpose of writing this review is to simplify the understanding of this rare disorder and review the best surgical protocols.

Pathogenesis

During 4 to 8 weeks of gestation, injury or maldevelopment of the developing structures of the sixth nerve nucleus leads to redirection of the branches from the third nerve to the lateral rectus. Review of literature shows that specific abnormalities in the anatomy of the extra ocular muscles have been observed. The lateral rectus has been found to be fibrotic and inelastic.[3,4] Co contractions of the medial and the lateral rectus muscle along with the fibrosis of the lateral rectus have been attributed to cause the retraction of the globe.

Various theories have been proposed explaining up shoot or down shoot. An upshoot is an over action and down shoot is an over depression of the adducted eye which is seen in 25%-39% of cases of DRS.[5,6,7] The upshoots and down shoots can be ascribed to mechanical and innervational causes[8]. Mechanical theory – the eye remains in the horizontal plane but as it adducts an up shoot or down shoot occurs abruptly due to side slip of the tight lateral rectus muscle. Innervational theory – it says that the eye gradually moves up or down during adduction due to the co innervation of the vertical rectus muscle with the lateral rectus muscle. The upshoots and down shoots seen in DRS are due to the anomalous innervation along with the bridle or the tethering effect of the horizontal muscles, with some amount of slippage of the muscles. This is explained by the fact that with any amount of elevation or depression which occurs outside the primary position there is a change in the horizontal rectus in reference to the rotation of the globe causing the horizontal muscles to become elevators or depressors in addition to horizontal action thus producing up or down shoots. Surgical, anatomical, cadaveric and electromyographic studies show that it is a complex combination of the mechanical, anatomical, innervational and central nervous system disorders which lead to these clinical findings in DRS.

Associated anomalies

Literature reveals DRS is frequently associated with various congenital malformations linked to an insult during the embryogenic development. Pfaffenbach et al showed that the patients with sporadic form of DRS had 10-20% times greater risk of congenital malformations, [9] which could be divided into:·

- Skeletal- involving the palate and vertebral column
- Auricular- involving the external ear, the meatus and the semicircular canals
- Ocular – involving the extra ocular muscles and eyelids and ocular dermoids
- Neural – involving the nuclei of the 3rd, 4th & 6th cranial nerve
- Skeletal - In a study Marshman showed that the patients with DRS had a greater than 50% incidence of having associated skeletal, neural & ocular problems in their first degree relatives.[10]

Associated anomalies identified in all patients with DRS[10]

- Skeletal
- High arched palate – 7%
- Webbed toes -6%
- Supernumerary ribs – 3%
- Cleft palate – 2% • Pigeon chest – 2%
- Club foot – 2 %
- Prominent first thoracic vertebra -26 %
- Clinodactyly -2 %
- Overcrowded dentition – 2 %
- Auricular
- Deafness – 19%
- Ear tags – 2%
- Malformed auricular cartilage -2 %
- Ocular
- Ocular dermoids – 3%
- Hypoplastic optic disc – 2%
- Myelinated nerve fibers – 2%
- Latent or manifest latent nystagmus – 2%
- Neural
- Fourth nerve palsy – 2%
- Seventh nerve palsy – 2 %
- Mobius syndrome – 2 %
- Batten disease -2 %

Dr Ramesh Murthy
Hyderabad, India

- Cardiac – 3%
- Syndromes
- Crocodile tears – 6%
- Goldenhar syndrome -3 %
- Okihiro syndrome 3%
- Holt Oram syndrome- 2%
- Marcus Gunn / jaw winking – 3%

Associated anomalies in first degree relatives of all patients with DRS[10]

- Skeletal (relatives of 10% patients)
- Webbed toes especially second and third (relatives of 2% of patients)
- Crossover of fifth toe (relatives of 2% of patients)
- Polydactyly (relatives of 2% of patients)
- Absent distal phalanges (relatives of 2% of patients)
- Clinodactyly (relatives of 2% of patients)
- Cleft lip (relatives of 2% of patients)
- Spina bifida (relatives of 2% of patients)
- Flexion deformity of metacarpophalangeal joint (relatives of 2% of patients)
- Auricular
- Deafness (relatives of 10% of patients)
- Ear tags (relatives of 7% of patients)
- Malformed auricular cartilage (relatives of 2% of patients)
- Ocular
- DRS (relatives of 19% of patients)
- Strabismus (relatives of 10% of patients)
- Dermoids of lid (relatives of 2% of patients)z
- Cardiac (relatives of 4% of patients)

CLASSIFICATION

The various classifications proposed are as follows-

Lyle & Bridgeman classification [11]

Type A- Abduction more deficient than adduction, adduction causes globe retraction and narrowing of palpebral fissure.

Type B – Abduction is deficient but adduction is not.

Type C – Abduction is less deficient than adduction, adduction causes globe retraction and palpebral fissure narrowing.

Papst classification was based on abnormal co contraction according to EMG studies.[12,13]

Abnormal co contraction of

1) medial and lateral rectus
2) superior and lateral rectus
3) inferior and lateral rectus
4) lateral rectus and several other muscles

Malbarn classification [14]

Type 1 –palsy of abduction

Type 2 –palsy of adduction

Type 3 –limitation of depression and elevation without impairment of horizontal movements.

Huber's classification[15] (using the above classifications and EMG outcomes), it is the most accepted and widely used classification system.

Type 1 – Marked limitation of abduction with minimally defective or normal adduction, retraction of the globe and narrowing of the palpebral fissure in adduction and widening in abduction, EMG showing normal electrical behavior of the medial rectus, with peak impulses on adduction and defective impulses on abduction thus showing paradoxical innervation of lateral rectus. Patient presents with esotropia in primary position and ipsilateral face turn.

Type 2 – Marked limitation of adduction with exotropia of the affected eye, abduction normal or slightly limited, retraction of the globe and narrowing of the globe on attempted adduction, EMG showing normal medial rectus impulses, lateral rectus showing peak impulses on abduction and a second paradoxical peak on adduction.

Type 3 – Combined limitation or absence of both adduction and abduction, retraction of globe and narrowing of palpebral fissure on attempted adduction, EMG showing intense innervation of both medial rectus and lateral rectus whether in primary gaze, abduction or adduction. Also called as exotropic Duane's, there is contralateral face turn and exotropia in primary position.

EPIDEMIOLOGY

*Incidence: The incidence of DRS among strabismus patients varies from 1% - 4%. [16]

*Sex distribution: shows that there is a female preponderance ranging from 40% to as high as 65%.[17]

Laterality: The predilection for left eye involvement is as high as 67% in unilateral DRS cases as seen in Table 1.[6,11,14,15,19,20]

Bilateral DRS is seen to range from 10%- 24%. [6,11,14,15,19,20]

Table 1. Laterality of eye involvement in DRS

Authors / year	No. of patients	Females	Male	Left eye	Right eye	Bilateral
Pfaffenbach et al(1972) [17]	186	106(57%)	80(43%)	107(58%)	37(20%)	34(18%)
Kirkham(1970)[18]	126	82(65%)	44(35%)	76(60%)	28(22%)	22(18%)
Isenberg et al (1977)[6]	101	58(57%)	43(43%)	56(55%)	29(29%)	16(16%)
O'Malley et al(1982)[19]	97	60(62%)	37(38%)	54(55%)	26(27%)	17(18%)
Tredici & von Noorden(1985)[20]	70	28(40%)	42(60%)	36(52%)	17(24%)	17(24%)
Raab et al (1986) [5]	70	45(64%)	25(36%)	47(67%)	16(23%)	7(10%)
Ahluwalia et al (1988)[4]	20	11(55%)	9(45%)	11(55%)	5(25%)	4(20%)
Total	650	290(45%)	280(43%)	427(66%)	158(24%)	117(18%)

Types of presentation:

Literature shows Esotropia in primary position was the most common presentation in the patients with DRS. [6,11,14,15,19,20]

Table 2 . Frequency of types of DRS

Authors / year	No. of patients	Type I	Type II	Type III
O'Malley et al(1982) [19]	97	84(87%)	11(11%)	2(2%)
Tredici & Von noorden(1985)[20]	70	56(80%)	5(7%)	9(13%)
Raab et al (1986) [5]	70	56(73%)	1(1%)	20(26%)
Ahluwalia et al (1988)[4]	20	11(46%)	5(21%)	8(33%)
Total	257	207(81%)	22(9%)	39(15%)

Amblyopia and refractive errors: it was seen that the average incidence of amblyopia was 3% -25%, Hyperopia was the most evident refractive error seen. [6,11,14,15,19,20]

Approach and diagnosis:

Duane's retraction syndrome as described by Duane in his land mark article consists of following components:

1) Complete, or less often partial, absence of outward movement of the affected eye
2) Partial or rarely complete deficiency of movement ward of the affected eye
3) Retraction of the affected eye into the orbit when it is adducted
4) A sharply oblique movement of the affected eye either up and in or down and in when it is adducted
5) Partial closure of eye lid (pseudo ptosis) of the affected eye when it is adducted
6) Paresis or at least marked deficiency of convergence, the affected eye remaining fixed in the primary position while the sound eye is converging

Head posture is also an important sign. A combination of the clinical features should be looked for and not a single sign.

Differential Diagnosis:

1) Abducens nerve palsy: it can be differentiated from DRS as in abducens palsy there is normal adduction with preservation of convergence, it is an acquired esotropia where the patient complains of diplopia and it does not have any up shoots or down shoots or any co-contraction of the globe.
2) Mobius syndrome: also called as congenital diplegia it is characterized by unilateral or bilateral limitation in abduction, adduction and convergence. The patient has mask like facies with associated anomalies of the chest, limbs and tongue; it occurs due to paralysis of the sixth and the seventh nerve, the patient with Mobius syndrome will not have up shoots, down shoots or any retraction of the globe. However it poses to be a diagnostic challenge to patients with bilateral Duane's.
3) Congenital or infantile esotropia: in a patient with congenital esotropia the deviations are larger than in patients of DRS. A doll's eye maneuver would elicit any abduction limitation and if this maneuver is not possible, patch test would be helpful in eliciting the abduction deficit.
4) Congenital oculomotor apraxia: children with congenital oculomotor apraxia have characteristic jerky horizontal head thrusts, but the children have normal vertical and full random eye movements.

Clinical Examination:

One should always ask the patient to fix in the best possible position so that the presence or absence of fusion can be determined. Office examination should include the cover uncover test in all the gazes as this affects the management strategy, presence of globe retraction, narrowing of palpebral fissure (one of the least dependable signs in DRS), look for up shoots and down shoots (which is due to the anomalously innervated LR slipping over the globe), co contraction of the globe (which is due to the LR muscle slippage above and below the globe) and presence of patterns.

Forced duction and forced generation test – this test helps to differentiate whether a muscle is tight or not; in DRS the muscle is tight due to long standing fibrosis whereas in acquired causes like sixth nerve palsy the muscle would not move voluntarily but would move without any restriction on forced duction test.

Surgical Teatment

Indications for surgical treatment

Absolute indications:

1) Presence of deviation in primary position
2) Presence of abnormal head posture
3) Severe co contraction of the globe

Relative indications:

1) Marked retraction of the globe on attempted adduction
2) Severe down shoot or up shoot on attempted adduction
3) To increase the binocular diplopia free field
4) To increase the rotational movement of the abduction in the affected eye

Surgical options:

1) Horizontal muscle surgery- recession or resection:

Recession of the tight and over acting muscle is a simple and an effective procedure, though it does not normalize the motility of the eye but if done meticulously it can improve the abnormal head

posture, can reduce the co- contraction of the globe and to some extent can improve the up shoots without breaking the fusional ability. The appropriate muscle to be recessed can be judged by the eye which has most marked limitation in adduction or abduction and whether there is any tropia in primary position. If there is esotropia, the medial rectus of the eye with limitation in abduction is recessed. If exotropia is present, then the lateral rectus of the eye with limitation in adduction is recessed. As far as possible a resection of the horizontal rectus muscle should be avoided because a resection increases the risk of enophthalmos and is more traumatic than a recession. Moreover a resection in DRS produces little improvement in the abnormal head posture but markedly reduces the ocular motility and increases the up shoots, down shoots and co- contraction of the globe. Thus a resection alone or with a recession can be performed but the surgical outcomes are very variable.

Transposition of muscle:

Transposition of the superior or the inferior rectus muscle towards the lateral rectus has been described.[21,22] This procedure has been known to increase abduction though adduction is sacrificed to some extent. This procedure may produce diplopia in 10-15 % of cases.[22] The surgery also has the risk of anterior segment ischemia. Literature search shows that the success rate of transposition surgery is 50- 75% in eliminating the abnormal head posture. Failures and over corrections of 30% with non correction of esotropia have been seen.[23]

Posterior fixation suture:

Posterior fixation suture (Faden) along with recession of appropriate rectus muscle surgery has been advocated. However the posterior fixation suture in the lateral rectus muscle produces gratifying results by eliminating the up shoots, but when done on the contralateral medial rectus in order to correct lateral incomitance was not satisifactory. [24]

Managing up shoots, down shoots, A or V patterns:

The various types of the up shoots or down shoots produced are[25]

A) In straight adduction and in adduction and elevation leading to an up shoot and a V pattern
B) In adduction and in adduction and depression causing a down shoot with an A pattern
C) A combination of the two producing a X pattern

One way of managing an upshoot or down shoot is to recess the lateral rectus muscle, the amount of recession to be done is based on the stiffness of the lateral rectus muscle assessed by forced duction test and whether the muscle is found fibrotic during the surgery. Recessing a very stiff muscle can significantly reduce the overshoots. If the lateral rectus muscle is non fibrotic and non stiff on forced duction test a large recession can achieve a similar result. Another approach to correct the shoots can be a posterior fixation suture on the lateral rectus, with or without similar sutures on the medial rectus, along with appropriate recession of the muscle. Jampolsky gave a unique surgical technique in which he showed that splitting of the lateral rectus muscle into Y configuration helped in reducing the globe retraction on adduction.[26] The lateral rectus was split into two, 10 mm posterior to the insertion and was reattached to the sclera, forming a Y pattern, all the patients showed an improvement of head turn, esotropia, upshoot or down shoot.[27]

Adjustable suture technique:

This technique was recommended by Pressman and Scott who performed a lateral rectus recession with an adjustable suture, though the literature shows that the results were not favorable.[28]

Botulinum toxin:

It was adopted as one of the non surgical modalities in order to correct esotropia in DRS but it was found to be ineffective.[29]

Complications of surgery:

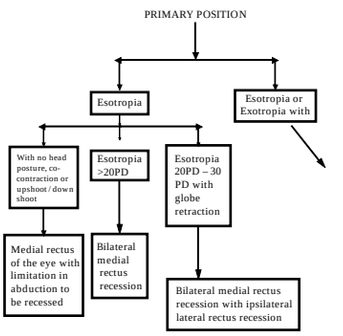
The possible complications that can occur in surgery are-

a) Anterior segment ischemia – this is seen usually after transposition of one of the horizontal recti to the lateral rectus along with recession or resection of other muscles, one way to prevent is to perform the recession or resection after 4- 6 months of transposition surgery.
b) If a large recession of medial rectus is performed then it can compromise adduction and produce exotropia postoperatively.
c) Other outcomes that can be un-desirous for the patient is persisting abnormal head posture, enophthalmos resulting in an attempt to correct the co- contraction of the globe and limitation of the movements.

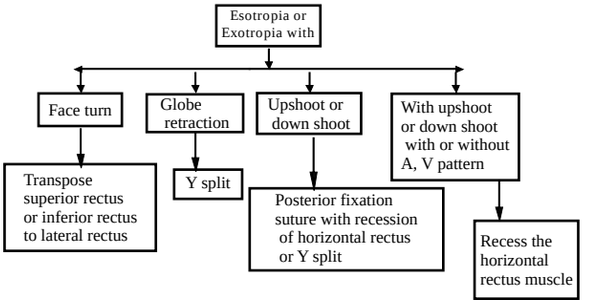
Surgical algorithm:

Based on primary position

Based on presence of face turn, abnormal head posture, upshoots, down shoots with and without A or V pattern



Points to be kept in mind –
A single recession cannot normalize motility of the eye
It can correct head posture to some extent
Can correct upshoot or down shoot with minimally risking the vertical tropias
A recession should always be preferred over resection as recession causes less enophthalmos
Resection should also be avoided as it reduces motility while increases upshoots or down shoots and co-contraction



Points to remember –
To identify if the upshoot is innervational or mechanical, if innervational it can be taken care by vertical rectus recession
Transposition of vertical rectus is a beneficial procedure but the risk of anterior segment ischemia is high

Synopsis:
Duane's retraction syndrome is a complex clinical entity whose diagnosis is based on the group of clinical signs and not just one, these clinical findings are due to abnormalities in the central nervous system and innervational problems which may be mechanical leading to long standing fibrosis of the muscle, or can be innervational. There is a strong co-relation between DRS and associated congenital anomalies in patients and their first degree relatives as shown in the literature. In patients with DRS there is a high predilection among females, they are usually hyperopic with or with out amblyopia and anisometropia, with typical presentation of Duane's type -1 being more common. There is a chance that it can be mis-diagnosed as congenital lateral rectus palsy but a good clinical examination with proper checking of movements can clinch the right diagnosis. As far as classification is concerned though the Huber classification is the most widely used one but the clinical variants do occur so these variants can be labeled as atypical Duane's. If there is an indication of surgery like a significant abnormal head posture, a noticeable ocular deviation, or severe contraction of the globe then the appropriate muscle should be operated upon and it yields a good clinical result. Though it has been more than 100 years since Duane's described this clinical entity, there is a long way to go to as far as surgical outcome is concerned.

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Legends for figures:

Figure 1:

1a: An 8 year old girl presented with left type 1 Duane's retraction syndrome. She was noted to have a right face turn at presentation.

1b: On primary gaze, the child was noted to have a small angle exotropia.

1c: On attempted left gaze, there was abduction limitation and enlargement of the palpebral fissure.

1d: On adduction, there was narrowing of the palpebral fissure and upshoot of the left eye.

Figure 2:

2a: In cases with upshoots or downshoots, Y split of the rectus muscle is an effective procedure. The muscle is split with a teaser hook.

2b: The muscle is then secured with 6-0 vicryl sutures and the 2 ends are secured about 12 mm away from each other at the desired position of recession.

Figure 1a

Figure 2a

Figure 2b

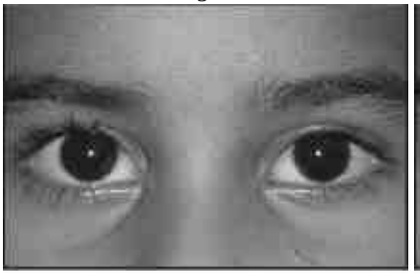

Figure 1 b

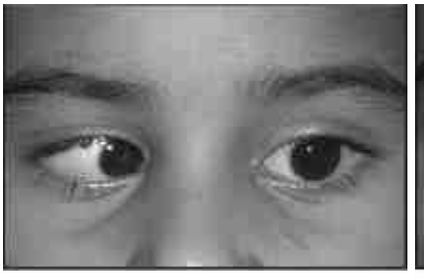

Figure 1c

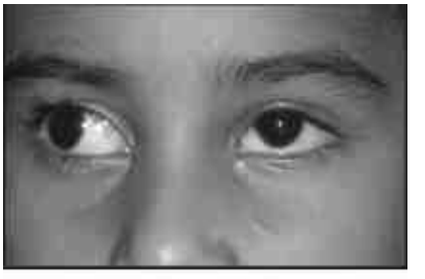

Figure 1d

Case Report

Metabolic cataract in cerebrotendinous xanthomatosis

Dr. Minu Ramakrishnan, Dr. Shobana Mallya, Dr. Shriwas S.R.

Abstract:

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive disorder of bile acid synthesis which is caused by impaired hydroxylation of cholesterol sidechains due to deficiency of mitochondrial enzyme sterol 27-hydroxylase (CYP 27). This deficiency of CYP 27, which is a key enzyme in the synthesis of chenodeoxycholic bile acid, leads to storage of cholestanol and cholesterol in many tissues, especially the lens of the eye, central nervous system and tendons. The disease manifests towards the end of the first decade and progresses slowly. Laboratory diagnosis is by elevated serum cholestanol levels as well as excessive urinary excretion of bile alcohols. Four diagnostic clinical hallmarks include premature bilateral cataracts, intractable diarrhoea, neurological signs and symptoms and tendon xanthomas. We describe a 25 year old patient with bilateral cataracts, cerebellar signs, tendon xanthomas and progressive mental subnormality in whom delayed diagnosis lead to worsening of neurological symptoms.This case attempts to highlight the importance of early diagnosis and treatment of CTX, since it is a rare but one of the few treatable childhood dementias if detected early.

Keywords:
Metabolic cataract, CTX

Introduction:

CTX was described for the first time in 1937 by Van Bogaert et al.[1] More than 20 different mutations have been identified in the gene encoding sterol 27-hydroxylase. Defect in this enzyme leads to decreased bile acid biosynthesis which leads to accumulation of 7α-hydoxylated intermediates, one of which is a precursor to cholestanol.[2] Patients present with cataract (as early as 5-6 years), mental retardation, cerebellar and pyramidal signs, seizures and tendon xanthomas especially on tendoachilles. Chronic diarrhoea as a prominent manifestation of CTX is also well described in early childhood. Successful treatment with chenodeoxycholic acid 750-1000 mg with or without a βHMG-CoA reductase inhibitor (Simvastatin) reduces formation of cholestanol and its deposition. Treatment stabilizes the manifestations and may show reversal of neurological as well as nonneurologic manifestations, provided an early diagnosis is made.[3] Here we report a case of CTX with all the characteristic features, with no diarrhoea.The patient had presented previously to an ophthalmologist with metabolic cataract and history of seizures but the diagnosis was overlooked, with no improvement in his clinical condition.This case highlights the need for thorough systemic evaluation and necessary laboratory investigations in reaching a diagnosis in such cases, so early treatment can be instituted.

Dr. Minu Ramakrishnan
K.J.Somaiya Hospital, Mumbai

Case History:

A 25-year old male presented to our medical outpatient department with cerebellar signs, epilepsy, tendon xanthomas and gradually progressive mental subnormality. He was referred to our ophthalmology department for gradual diminution of vision in both eyes, right > left. He was a product of full term normal delivery, born of nonconsanguinous marriage. None of his siblings had any similar complaints. The patient was on treatment for epilepsy since childhood and had consulted an ophthalmologist also, but a diagnosis of CTX was not reached at that time.

On ocular examination, visual acuity in the right eye was counting fingers at 3 meters-not improving with glasses or pinhole, and in the left eye was 6/60, improving to 6/24 with dilatation. He had bilateral horizontal pendular nystagmus, so manual occlusion of eye with palm of the hand with head position at null point of nystagmus was used for testing each eye individually. As patient had only mild mental retardation, patient could comprehend both the Landolt C chart and the Illiterate E test. Dilated slit lamp examination revealed a stellate type of anterior and posterior sub-capsular (PSC) cataract in the right eye (Fig. 1) and only an early minimal central PSC cataract in the left eye. Dilated refraction and fundus examination were unremarkable.

Systemic examination revealed bilateral pes cavus, presence of cerebellar signs (left more than right), generalized muscle wasting, brisk reflexes with normal tone and prominent tendoachilles (Fig. 2). On detailed investigations -electroencephalogram showed evidence of hyper excitability, serum lipids, serum eptoin were within normal limits. Fine needle aspiration cytology of Achilles tendon showed foamy cells and giant cells-suggestive of xanthoma with no myopathy, MRI Brain showed Cerebellar and cervical cord atrophy and hyperintensity in the region of dentate nucleus of cerebellum (Fig. 3). MRI Achilles tendon showed patchy appearance of xanthoma with intermediate signal intensity on T1 images (Fig. 4).

Psychiatric evaluation showed an intelligence quotient of 60 on Vineyard Social Maturity Scale.

A diagnosis of CTX was made, based on clinical features and MRI findings. Main differential diagnosis was Marinesco-Sjogren syndrome, in which, in addition to these features, muscle shows autophagic vacuolar myopathy, which was absent in this patient. Other differential diagnosis considered were cataract dental syndrome, cataract-ataxia-deafness syndrome, galactosemia and oculocerebral syndrome of Lowe. They were ruled out by absence of any other systemic features and the presence of tendon xanthomas that are characteristic of CTX. Due to financial constraints genetic workup and serum cholestanol levels could not be done.

Once diagnosis was established, patient was started

on ursodeoxycholic acid 750 mg/day. Chenodeoxycholic acid, which is considered better for treatment, was not available. Long-term follow-up of the patient is awaited. The patient was taken up for right eye cataract surgery.Right eyemanual small incision cataract surgery (Sutureless) with successful in the bag placement of posterior chamber lens was performed.Post operative best corrected visual acuity in the right eye improved to 6/24. Left eye had only minimal cataract, for which no intervention was done. Though the conjunctiva and sclera were unusually rigid and resistant to cutting with scissors and blades, biopsy of these tissues did not reveal anything specific.

Discussion:

Metabolic cataract with progressive mental subnormality should be evaluated to rule out this treatable disorder. Chronic diarrhoea, tendon xanthomas, other neurological symptoms as well as atherosclerotic vascular disease[4] and osteoporosis[5] may be associated findings. Other ocular findings occasionally reported in literature include pale optic disc and signs of premature retinal senescence, which were absent in this case[6]. 27-hydroxylase deficiency leads to xanthomas in normocholesterolemic humans, whereas deposition of cholestanol and cholesterol in brain leads to severe symptoms. Diagnosis can be confirmed by serum cholestanol (Normal values: 3.3-12.5µmol/lit)[7] and sterol 27-hydroxylase assay as well as by typical MRI feature showing cerebellar hyper intensity in the region of the dentate nucleus. This is due to axonal damage and demyelination caused by the lipid-laden xanthoma present in the region, which usually is seen as a hypo intense shadow surrounding the dentate hyper intensity on MRI.[8]Surprisingly, xanthomas are missing in about 30% of patients with CTX[9].

Treatment with chenodeoxycholic acid has been favorable. Some authors claim that the condition stabilizes with treatment, but there is no significant improvement in neurological deficit [4, 9], whereas others claim successful reversal of symptoms on long term treatment especially with early diagnosis.[2]Even cataract is reported to stabilize with treatment.[10] Although long term follow-up is not available in this case, our aim is to highlight the role of the ophthalmologist in evaluating patients with metabolic cataracts, so that not just the cataract can be treated early, but also for early referral to the treating physician for early diagnosis and prompt treatment which can reverse the psychomotor changes in these patients.

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Figure 1: Diffuse illumination showing metabolic cataract in the right eye.

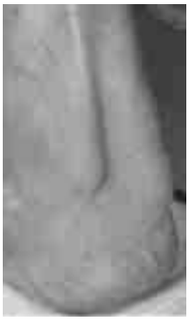

Figure 2: Lateral aspect of ankle joint showing the prominent tendoachilles.

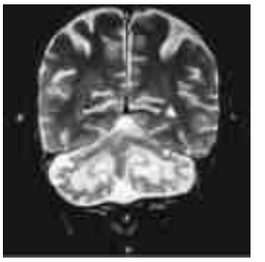

Figure 3: Coronal T2-weighted image showing low signal intensity in the dentate nucleus.

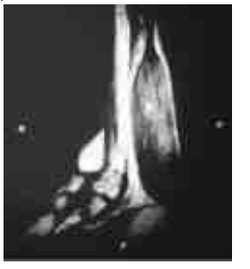

Figure 4: Sagittal T1-weighted image of Achilles tendon showing a gross morphologic mass with intermediate signal intensity.

Recent advances and future vistas in treatment of diabetic retinopathy

Dr Minu Ramakrishnan, Dr Ajay Dudani

India heads the G-8 countries with the highest number of patients with diabetes. In 1990, there were 15 million diabetics in India, which is increasing by leaps and bounds. Out of this diabetic population, it has been estimated that atleast 28.85% of diabetics will have diabetic retinopathy (DR) irrespective of duration of diabetes. From the cohort of UKPDS data, among 4209 newly diagnosed persons with Type 2 (DM), the initial examination showed that diabetic retinopathy (DR) was present in 37% of subjects. For a disease reaching such epidemic proportions, a multi-pronged approach is necessary to prevent blindness.

Advancements are occurring at all stages of management - diagnosis of retinopathy, systemic control to prevent / delay onset of retinopathy, laser treatment, intravitreal injections and finally the surgical management for eyes with severe retinopathy.

Advances in diagnostic modalities:

1) Ultrawide field fluorescein angiography:
   As compared to existing fundus cameras, this model captures 200° fundus images, upto the peripheral retina so that entire retina can be scanned by a single photograph. This is done using an Optos P200MA scanning laser ophthalmoscope.
2) OCT (Optical Coherence Tomography)
   The high speed spectral domain OCT allows accurate retinal assessment over a period of time. Current OCT systems provide quantitative assessment of a single anatomic compartment i.e. retinal thickness or volume. Automated quantification of individual retinal layers is of use in diabetic macular edema, but it is not possible with current software.
   Advances in OCT hardware will allow functional information, of particular significance in DR , to be obtained[1]. Using Doppler techniques in combination with OCT, direct measurement of retinal blood flow will be possible, as will depth-resolved localization of retinal blood vessels. In addition, efforts are underway to obtain information regarding metabolic status of tissue by employing spectroscopic techniques in combination with OCT.
3) Telemedicine and DR screening:
   There is evidence that implementation of surveillance programs for DR results in increased overall assessment rates for patients with diabetes [2,3]. Additionally, studies have shown that identification of vision-threatening disease with systems for DR assessment results in increased treatment rates[3] and excellent compliance with recommendations for referral[2].

Prevention / Systemic Management:

The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have demonstrated that optimal metabolic control could reduce the incidence and progression of DR[4,5].

1) Good blood sugar control (medical/ surgical/genetic interventions):
   In the last decade, insulin analogues have been developed with improved insulin action. Better technology in administering insulin (e.g. inhaled insulin) and monitoring glucose levels , as well as newer drugs like exenatide, a thiazolidinedione that enhances glucose-dependent insulin secretion, promise a better future for our diabetic population.
   Gastrointestinal surgeries, like ileal transposition, pancreatic transplantation has been shown to be effective in reducing blood sugar levels, especially in patients with Type 1 DM.
   Three genes have shown promising results in the search for markers for DR - the ALR 2, VEGF polymorphisms and the Receptor for Advanced Glycation End Products gene. According to several ongoing genome-wide association studies (GWAS), genetic variants associated with risk of Type 2 DM include loci on / near genes IGF2BP2, CDKAL 1, CDKN2A, CDKN2B, TCF7L2, SLC 30A8, HHEX, FTO, PPARG and KCNJ 1L[6] . In future, these genes can be modified using vectors to prevent retinopathy.

2) Rigid control of hypertension:
   This is also effective in reducing progression of retinopathy. The UKPDS showed that for DR, the level of blood pressure is important and not the type of drug used[7]. Of the treatment options available, ACE inhibitors (that inhibit the renin - angiotensin system) have shown experimental evidence of its role in DR. DR Candesartan Trials (DIRECT) is designed to establish if treatment with angiotensin receptor blocker candesartan cilexetil, can effectively inhibit onset and progression of Dr[8].
3) Aldose Reductase Inhibitors (ARIs):
   In animal studies, ARIs have been useful in preventing DR if administered from the onset of diabetes [9].The one long-term study in humans using sorbinil was ineffective, possibly because

Dr. Ajay Dudani
Zen Eye Centre, Khar, Mumbai

the drugs used were having problems with potency and safety. A new drug, ARI-809 has been tried in animal studies and was highly effective in preventing and /or reversing retinal neuroglial abnormalities in diabetic rats[10].However, further work is required to examine its therapeutic effect on long-term diabetes-induced retinal vascular damage, and it is yet to be tested in humans.

4) Protein Kinase C (PKC) inhibitors:
It has been demonstrated that diabetes- induced PKC β 1/2 activation contributes to the development and progression of DR through various mechanisms, such as smooth muscle contractility, basement membrane protein synthesis, endothelial permeability and angiogenesis[11].
In animal studies, ruboxistaurin mesylate, a novel, highly selective inhibitor of PKC β 1/2 ,has demonstrated the potential to prevent DR[11-13]. Two multicenter, placebo-controlled, Phase 3 clinical trials were carried out initially: the PKC DR study (PKC DRS) and the Diabetic Macular Edema Study (PKC- DMES)[11-13]. The PKC-DRS trial found no significant beneficial effect of ruboxistaurin on the progression of DR or the need for laser photocoagulation, but it did reduce sustained moderate visual loss by more than 40% compared with placebo.
One concern with ruboxistaurin is that it could worsen DR because inhibition of PKC β 1/2 accelerates apoptosis of pericytes exposed to high glucose[14].

5) Benfotiamine:
This is a thiamine derivative, which acts by activating the pentose phosphate pathway enzyme- transketolase, which converts glyceraldehydes-3-phosphate and fructose-6-phosphate into pentose-5-phosphates and other sugars. It has been reported to prevent DR in diabetic rats[15].However, further research is required for human trials, and a clinical trial is underway to test the potential of benfotiamine to combat DR.

6) Anti- inflammatory drugs:

- Minocycline:
Early evidence suggests that minocycline, an antibiotic with anti-inflammatory properties, blocks the activation of microglia and prevents DR[16].
Minocycline reduces diabetes-induced inflammatory cytokine production and the release of cytotoxins from activated microglia, and also significantly reduces caspase-3 activity within the retina. Thus, minocycline is a strong candidate for further consideration as a therapeutic drug to prevent DR, but further studies are needed to qualify its effects.
- Aspirin/Dipyrimadole/ Sulfasalazine:
Data from animal studies have demonstrated the potential of aspirin to prevent DR. High doses of aspirin (2mg / kg / day) prevent leucocyte adhesion to the retinal endothelium via reduction in the expression of integrins, intracellular adhesion molecule-1, endothelial nitric oxide synthase activity and TNF- K production in diabetic rats[17]. Only 2 large human trials of aspirin for DR have been reported. The joint French-UK aspirin and dipyridamole trial (5 yr RCT) showed fewer new microaneurysms formed in patients on aspirin alone 330mg tds or in combination with dipyrimadole 75mg tds[18]. Although findings were statistically significant, there was only a slight beneficial effect. A much larger ETDRS trial found that a daily dose of aspirin 650mg had no effect in 3711 patients allocated randomly to active treatment or placebo[19](but this study had patients with much severe retinopathy than the previous one). On the evidence till now, high-dose aspirin may prove useful as a preventive treatment in DR, but further trials are needed. Recent trials with sulfasalazine, a representative of the salicylates, administered to diabetic rats inhibited diabetes-induced upregulation of several nuclear factor-kB-regulated inflammatory gene products, and also apoptosis and formation of acellular capillaries[20].

7) Somatostatin Analogues:
On observing that DR regressed in a postpartum woman with spontaneous pituitary infarction, hypophysectomy was suggested as a potential treatment for DR and this was supported by small clinical trials [21,22].This led to the development and testing of long-acting analogues of the naturally occurring peptide- somatostatin, to prevent DR[22].Although in experimental models somatostatin has been shown to be a potent inhibitor of neovascularization, further clinical evidence from larger treatment groups of longer trial duration is required. In a small-scale randomized controlled study of 23 patients with severe Non Proliferative DR (NPDR) or early PDR, octreotide (a long-acting somatostatin analogue) reduced the need for laser photocoagulation compared with conventional treatment . Two large-scale multicenter,randomized placebo-controlled clinical trials initiated by Novartis (Basel, Switzerland) have been inconclusive on the effect of octreotide on the progression of retinopathy, but appeared to demonstrate some benefit in visual acuity

Advances in Laser Photocoagulation:

Although laser photocoagulation is usually the recommended treatment for proliferative DR (results of DRS demonstrated that panretinal photocoagulation effectively reduces the risk of vision loss in almost 60% patients with DR [24,25],and according to the ETDRS trial, macular laser photocoagulation reduced the risk of vision loss by 50% in patients with clinically significant DME), retinopathy continues to progress despite laser, and treatment must be repeated in many patients. Furthermore, photocoagulation is an aggressive technique with considerable limitations and adverse effects, as it destroys the neural retina, leading to decreased contrast sensitivity and loss of peripheral and night vision. Therefore, the development of noninvasive therapies to prevent and treat diabetic retinopathy is necessary and remains a priority for eye research.

Lasers are being improved, e.g.- use of subthreshold diode micropulse (SDM) effectively treats severe NPDR and PDR without causing laser-induced retinal damage and the complications associated with conventional photocoagulation[26].It produces clinically invisible scars, with functional advantages being absence of scotomas, preservation of colour vision and contrast sensitivity [27].

Also, the use of multispot pattern scan laser (PASCAL) which uses high power with brief exposure times, has shown to cause less collateral damage, is less time consuming and less painful to the patient with similar retinopathy regression when compared to standard laser treatment[28].

Currently, several clinical trials are underway to compare the efficacy of laser with other treatments like steroids and intravitreal anti Vascular endothetial growth factor (VEGF) drugs. There are also studies evaluating combination therapy to determine whether there are any additional benefits in terms of efficacy and interval of treatments. (e.g.- The Ranibizumab for Edema of the Macula in Diabetes Study, The Diabetic Retinopathy Clinical Research network phase 3 trial ,etc).

Intravitreal injections and implants:

1) Corticosteroids:

Steroids prevent blood-retinal barrier breakdown and inhibit the production of VEGF, as well as certain matrix metalloproteinases.

Triamcinolone acetonide (TA), a slow–release steroid, is an emerging therapy for diabetic macula edema (DME) that suppresses inflammation, reduces vascular leakage and inhibits fibrovascular proliferation[29,30]. Edema often improves after injection and also the visual acuity. However, the treatment effect lasts only approximately 6 months and there is a limit on how often it is safe to enter the vitreous cavity. The Triamcinolone for DME Study (TDMO)[31] evaluated IVTA treatment safety and efficacy specifically in patients with persistent DME despite laser treatment. It showed significant improvement, with beneficial effect lasting up 2 years in the study. The Diabetic Retinopathy Collaborative Research Network (DRCR.net) Study [32] compared safety and efficacy of IVTA(1 mg/ 4 mg) with laser treatment. All 3 groups showed improvement in retinal thickness and visual acuity, but laser treated group had fewer adverse events compared to IVTA-treated eyes. The half life and adverse effects of IVTA have been shown to be dose-dependent, with no change in efficacy, hence 1 mg TA is preferred to 4 mg injection.

Administration of TA by intravitreal injection is also an effective treatment for proliferative DR (PDR), with the most common complications of treatment being raised intraocular pressure and intraocular infection [33].

The new I-vation implant is an intravitreal implant with controlled release of triamcinolone acetonide. In vitro studies have shown that drug release is controlled by a parabolic differential equation, which describes its drug diffusion in a durable polymer matrix [34] . Clinical trials are awaited for *in vivo* results.

The fluocinolone acetonide implant, Retisert is being investigated for the management of DME with promising results [35].

Another corticosteroid proving effective for the treatment of persistent DME is dexamethasone [36], which has been recently developed by Allergan (Posurdex) as a biodegradable implant, and is being evaluated for possible lower risk of steroid-related adverse events than triamcinolone.

2) Anti- VEGFs:

Based on experimental evidence, there has been great interest in the development of anti-VEGFs for the treatment of PDR and Age related Macular Degeneration (ARMD.)

Pegaptanib (Macugen) is an intravitreally administered 28-base RNA aptamer that selectively binds VEGF 165, prevents vascular permeability and neovascularization in PDR [37]. A recent double-masked, multicenter, Phase 2 clinical study showed that patients receiving an intravitreal injection of pegaptanib every 6 weeks demonstrated stabilization or improvement in visual acuity, reduction in the central retinal

thickness and were less likely to need additional therapy with photocoagulation at follow-up [38].

Bevacizumab, a recombinant humanized monoclonal antibody that binds all isoforms of VEGF with high affinity, has also been shown to cause regression of new blood vessels when used intravitreally for PDR and ARMD [39,40].

Ranibizumab, a recombinant, humanized, monoclonal antibody active against all VEGF isoforms, has also shown promise. Intravitreal injection of 4 doses over 6 months into 10 patients with diabetic retinopathy showed a dramatic 85% reduction in the thickness of their maculas, and improvement in visual acuity by atleast 2 lines on the standard eye chart [41].

Clinically, intravitreal injection of anti-VEGF has a well-recognized risk of endophthalmitis, with a prevalence of 0.3% per injection [42]. However, recently, Berglin and colleagues [43] have demonstrated that human and rabbit sclera are permeable to bevacizumab and ranibizumab, suggesting that transcleral drug delivery could be a viable alternative.

Other approaches under trial to block VEGF include VEGF Trap and si RNA, Bevasiranib. VEGF trap acts as a receptor decoy by binding to all the isoforms of extracellular VEGF[44]. Do et al [45] recently reported the phase 1 results in 5 patients with DME who received 4 mg VEGF Trap, which are encouraging, and larger phase 2 trials are underway. Bevasiranib is designed to inactivate VEGF mRNA and essentially silence the genes responsible for production of all VEGF isoforms. Theoretically, one bevasiranib molecule can eliminate the production of thousands of VEGF proteins, and thus provide longer duration of VEGF blockade with less frequent injections. But one limitation is that it does not affect the active VEGF protein already present, it only inhibits the production of future protein products. This is seen in the RACE trial, a phase 2 RCT for RNAi Assessment of Cand5 in patients with DME, which showed initial deterioration of visual function and increased retinal thickness in the first 4 wks, followed by improvement and 91% showed stabilization by 6-12 wks[46] . In the phase 3 trial, ranibizumab will be used to initiate therapy followed by intravitreal injections of bevasiranib every 8 or 12 wks thereafter.

Surgical treatments:

1) Sutureless vitrectomy:
Most conditions in DR can be easily operated with small gauge vitrectomy, typical indications being vitreous haemorrhage and tractional retinal detachment. Small gauge (23G, 25G) vitrectomy provides decreased sclera trauma, postoperative inflammation and postoperative morbidity, and a low incidence of postoperative complications. These advantages are contributing to the trend for earlier surgical intervention for a number of diabetic indications. Only cases which require sclera buckling or pars plana lensectomy from the outset or cases with severe anterior Proliferative vitreo Retinopathy (PVR) with combined tractional/ rhegmatogenous Retinal detachment (RD) are best approached with 20 G surgery for maximum instrument excursion required for these surgeries.

2) Chemical PVD Induction:
The vitreous plays a significant role in the development of PDR, as the new vessels use the posterior vitreous face as a scaffold. The retracting vitreous pulls on these vessels and is responsible for both vitreous haemorrhage and retinal detachment. Vitreolysis, using hyaluronidase has been tried effectively and shows no toxicity [47]. However, it has not been approved for clinical use by FDA. Also, hyaluronidase causes vitreous liquefaction, but several animal studies have failed to demonstrate Posterior vitreous detachment (PVD) induction after intravitreal hyaluronidase injection.
Other potential enzymes that may allow nonsurgical treatment for DME and PDR include plasmin and microplasmin[48,49]. Microplasmin induces PVD in a dose-dependent manner in animal models as well as postmortem human eyes[50], and human trials are currently underway in United States and Europe.

3) Preoperative Intravitreal Bevacizumab injection:
Bevacizumab (1.25 mg) is used to facilitate vitrectomy in severe PDR. In cases with active neovascularization, the use of bevacizumab appears to reduce the risk of intraoperative bleeding, facilitating the removal of fibrovascular membranes[51]. Vitrectomy is done one week after intravitreal injection, this allows for some regression of neovascular tissue when vitrectomy is undertaken, but one disadvantage is that neovascular tissue may contract and cause Tractional RD (TRD) if surgery does not proceed in a timely manner[52].

4) Injectable Rapamycin (Sirolimus):
Rapamycin has anti-inflammatory, antifibrotic, antipermeability, antiproliferative and antiangiogenic effects. A phase 1 trial reported 50 patients with DME randomly assigned to a single intravitreal or a single subconjunctival rapamycin

injection. Results showed statistically significant functional and anatomical improvement at 90 days, which persisted through 180 days[53]

Availability of all these exciting options for DR will definitely help in early detection and best possible systemic and ocular treatment, which will ensure that our dream that no diabetic will lose his sight to retinopathy is no longer just a dream, but a definite possibility.

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