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ASSESSMENT OF VISUAL CONTRAST FUNCTION AND EFFECTS OF CIT1COLINE TREATMENT IN CHILDREN WITH VISUAL IMPAIRMENT

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Assessment of visual contrast function and effect of citicoline treatment in children with visual impairment

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ABSTRACT

Purpose: The present studies address the questions if visual dysfunction in severely visually impaired children can be measured with contrast tests high or low, how it relates to their visual abilities assessed with behavioural methods and if visual function in these children can be improved by neuro-pharmacological treatment.

Methods: Twenty children aged 6-16 years from the Al-Maktoom school for visually impaired children in Islamabad, Pakistan were included in the first study and 22 children aged 6-14 years in the second study. The children were divided into two different groups of visual impairment. One group with congenital cataract, late surgery and inadequate postoperative treatment, causing vision deprivation amblyopia (VDA), and the other group with mainly retinal and optic nerve disease causing peripheral visual impairment (PVI). The intension was to compare the results of visual assessment in the two groups as a basis for suitable interventions based on the type of visual dysfunction.Both high and low contrast visual acuity was assessed, using cardboard letter charts. Previous studies in children with visual handicap had shown that visual function assessment with these tests corresponded quite well with assessment of the functional ability of the children.In the second study, all children received an intramuscular injection of 1 g of citicoline for 10 consecutive days. Both high contrast and low contrast visual acuity was tested with methods described earlier. Acuity was measured at baseline (day 1), on day 30 and on day 90. Such studies have not been performed in children with severe visual impairment and treatment effects of citicoline have not been examined.

Results: The distance high contrast tests were generally not well correlated among themselves in either group, whereas the near vision and low contrast tests were better correlated in the VDA group than in the PVI group. The low contrast tests were well correlated amongst themselves in the VDA group. It was also noted that the group with VDA had better functional ability to cope with the tasks put to them.In the second study an improvement in visual acuity of children with VDA was seen mainly during the period up to 30 days after citicoline treatment, while the improvement in the children with PVI occurred during a longer period, up to 90 days. A decline in acuity after treatment was observed in 2/11 children with VDA and 3/11 children with PVI.

Conclusion: For a broad evaluation of the visual capabilities of children with impaired vision it is suggested that the visual examination should include both high- and low-contrast tests and functional vision assessment. The results of this pilot study on Citicoline effects are encouraging but extended examinations are needed to determine treatment procedures for citicoline treatment of visual dysfunction in children with severe visual impairment.

LIST OF PUBLICATIONS

I. Siddiqui A, Rydberg A, Lennerstrand G.
Visual Contrast Functions in Children with Severe Visual Impairment and the
Relation to Functional Ability. Visual Impairment Research 7:43-52, 2005.

II. Siddiqui A, Rydberg A, Pansell T, Lennerstrand G.
Citicoline Treatment of Children with Visual
Impairment; a Pilot Study. Pak J Ophthalmol 2012, Vol. 28 No. 4

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LIST OF ABBREVIATIONS

PVI	Peripheral Visual Impairment
VDA	Visual Deprivation Amblyopia
Lshc	Lea Symbol High Contrast
Lnhc	Lea Number High Contrast
Slhc	Sloan Letter High Contrast
Nvlh	Near Vision Lea Hyvärinen
Lslc	Lea Symbol Low Contrast
Lnlc	Lea Number Low Contrast
Sllc	Sloan Letter Low Contrast
WHO	World Health Organization
VFQ	Visual Functioning Questionnaire
LH	Lea Hyvärinen

1   INTRODUCTION

The present studies address the questions if visual dysfunction in severely visually impaired children can be measured with contrast tests high or low, how it relates to their visual abilities assessed with behavioural methods and if visual function in these children can be improved by neuro-pharmacological treatment.

Tests for visual acuity at different contrast levels have been developed during recent years, but an evaluation of visual function with these tests in children with severe visual impairment has not previously been done, and the results from visual acuity testing have not been related to assessment of functional vision (Siddiqui et al., 2005).

Treatment for most diseases causing visual impairment in children is quite limited. To the lesions of the structures of the eye and brain is often added the effects of abnormal development of the visual brain. Recently drugs supporting recovery in neurological disease have been introduced and they have been used also in ophthalmology, particularly in glaucoma and amblyopia, but their effects on lesions causing visually impairment in children have not been studied (Gottlob and Stangler-Zuschrott, 1990; Leguire et al., 1993; Parisi et al., (1999); Fresina et al., 2008; Rejdak at al., 2002; Campos et al., 1995; Porciatti et al., 1998).

1.1   CAUSES OF VISUAL IMPAIRMENT IN CHILDREN

In the present studies performed in Pakistan, children with severely reduced visual function have been included but not children with total loss of vision and blindness. The spectrum of diseases encountered is that of the developing countries: genetic diseases, malnutrition, infections, tumours and trauma. The lesions are affecting different parts of the eye and the visual pathways. Some conditions are inborn, others are inflicted in the foetal stage or at a very early age, and still others occur during the first years of life (Siddiqui et al., 1996). In developed countries visual loss associated with brain damage due to injuries at birth is the single greatest cause of visual impairment in children.

1.2   DISEASES OF THE EYE AND BRAIN

Disorders of the eye and the anterior visual pathways affect the quality of the visual image. The main diseases of the eye in visual impairment of childhood include opacities of the optical parts of the eye, e.g. corneal opacities and cataract, inborn

diseases of the retina and optic nerve, abnormal development of the retinal vascular system in retinopathy of prematurity (Gogate et al.,2011).

Disorders of the posterior visual pathways including the primary visual cortex will affect visual processing and may also lead to visual field defects if the damage is unilateral, or to severely reduced vision if the lesions are bilateral. Disorders in the visual associative cortices are often patchy, affecting specific visual sub-functions, such as recognition of persons, perception of objects, size or directions, and of movement and speed of objects. The main causes of lesions in the posterior pathways are genetic disease or infections of the nervous system, and hypoxic ischemic insults both in full-term and preterm infants. However, visual dysfunction due to lesions of the posterior visual pathways may be compensated by mechanisms involving 'plasticity' of the infant brain, an essential factor in the apparent visual 'recovery' that is described so frequently in these children. It is possible that such improvements in function could be supported by neuro-pharmacological treatment.

As Dutton and co-workers have pointed out, children with hypoxic insults may have visual acuity and visual field loss coupled with specific visual disabilities attributed to damage to the dorsal stream system (parietal lobe) or ventral stream system (temporal lobe). Even more challenging are the children, who present with normal or slightly reduced acuities but with significant cognitive visual dysfunction (Dutton et al., 2006). The associative visual cortex areas contribute a significant portion of the visual disability in a number of children with brain damage and visual disability (Huo et al., 1999).

1.3 VISUAL DEPRIVATION - AMBLYOPIA

If abnormalities of the eye occur early in life, and if the obstacles to vision are not removed at an early age, the normal development of the visual brain is impaired, leading to deprivation of visual function. The reduced visual function can be reversed if treatment is instituted during the so-called sensitive period of visual development, the main part of which is occurring during the first 3 – 4 years of life. The condition of visual dysfunction that remains after no or insufficient treatment against visual deprivation is termed amblyopia. It has been well established through animal studies that amblyopia is represented by functional and morphological modifications in the lateral geniculate nucleus and the visual cortex. When amblyopia exists, it can be cured

if adequately treated in children less than 6-7 years of age, but even in older patients some visual improvement can be achieved with therapy (Noorden and Campos, 2002).

Combined with amblyopia is the phenomenon of crowding or separation difficulties, implying that small objects are easier to detect when they are presented in isolation than when they are included in a crowded surrounding. Crowding is observed also in other types of visual impairment, but is a more prominent feature in amblyopia (Noorden and Campos, 2002)

In the present group of children with impaired vision, the main cause for amblyopia and visual deprivation was congenital or early cataract that had been operated too late, i.e. after the age of 3 months, in combination with no or deficient postoperative amblyopia treatment.

1.4   PERIPHERAL VERSUS CENTRAL VISUAL IMPAIRMENT

The children in the present studies had visual handicap either mainly due to retinal and optic nerve disease or to congenital cataract operated late and with less than optimal rehabilitation, leading to visual deprivation and functional changes in the posterior visual pathways.

The children were subsequently divided into two different groups of visual impairment. One group with mainly retinal and optic nerve disease causing peripheral visual impairment (PVI) and the other group with congenital cataract, late surgery and inadequate postoperative treatment, causing vision deprivation amblyopia (VDA). The intension was to compare the results of visual assessment in the two groups as a basis for suitable interventions based on the type of visual dysfunction (Siddiqui et al., 2005)

2 TREATMENT METHODS

2.1 IN DISEASES OF EYE AND BRAIN

For eye diseases caused by infections and malnutrition effective treatment is available, although not sufficiently applied in developing countries due to limited resources of medical care. For inherited disorders of the eye and brain very limited medical treatment is available. Opacities of the optical media, as a result of corneal disease and cataract, can be removed by surgery (Siddiqui et al., 1996). Retinopathy of prematurity can be treated by different kinds of retinal surgery. Hypoxic brain insults may be prevented or reduced by adequate neonatal care. In rehabilitation for visual impairment different methods are used such as adaptation of light and colour of the environment to suit the kind of visual impairment, educational methods to use remaining visual function appropriately through compensating mechanisms.

Visual rehabilitation does not need to be extremely intricate and expensive strategies involving assistive devices.

The use of strategies as the Little room, utilizing the "Active Learning " technique maintain that children who are blind with additional disabilities learn best by being actively involved in their environment without direct adult intervention. Lilli Nielsen encouraged educators and families to design the environment in such a way that children are motivated to reach out and explore their surroundings (Newton, 2012). Good optometric and ophthalmic services are now helping most of the school going children whether in segregated (Special schools) or inclusive education in Pakistan (Siddiqui et al., 1996).

2.2 IN VISUAL DEPRIVATION- AMBLYOPIA

The treatment is directed towards reducing causes of vision deprivation by surgery at an early age for corneal opacity, cataract or any other condition, affecting the ocular media, followed by correction of refractive errors, including anisometropia. In conditions where one eye is better equipped than the other in terms of visual image quality, and suppression of the poorer eye is expected, different methods of stimulating vision of the poorer eye is instituted. The most efficient way of such amblyopia treatment is by occlusion of the better eye with a patch for different periods of time,

depending on the severity of amblyopia, but methods of pharmacological treatment has also been used (Noorden and Campos, 2002).

2.3   PHARMACOLOGICAL TREATMENT

Topical treatment with mydriatics is mainly done in amblyopia caused by strabismus and anisometropia. Blurring of the good eye with atropine as an amblyopia treatment has recently been shown to be as effective as conventional occlusion therapy
(Li and Shotton, 2009), Menon et al., 2008).

The effect of centrally acting neurotransmitters especially Levodopa on vision in amblyopia has been studied by Gottloeb and Stangler-Zuschrott (1990) and Leguire at al. (1993) and the results were   encouraging. However, the improvement of visual acuity declined after one month of medication (Gottloeb and Stangler-Zuschrott 1990; Leguire et al., 1993).
The side effects noted were few and mostly dose dependant.
The commonest side effects were nausea, tiredness, headache, earache and sore throat (Leguire et al., 1993).

Systemic treatment with citicoline has been used to improve vision in different types of eye diseases including amblyopia. Citicoline was first introduced in treatment of neurological disease such as stroke and traumatic brain injuries and it was found to improve the functional outcome and reduce neurological deficit. Citicoline is an intermediate metabolite in the major pathway for the synthesis of the membrane phospholipids and can support neuronal cell-membrane function that has been damaged by trauma, ischemic events, toxins, infections or neural degeneration (Parisi et al., 1999; Rejdak et al., 2002; Campos et al., 1995).

Patients in the studies of neurological impairment have reported that colors were brighter and that visual contrast was enhanced, which have led to investigations of citicoline effects in various ophthalmic conditions. Studies in patients with glaucoma have suggested that citicoline repairs damage to the optic nerve and the retina.

Citicoline was found to significantly improve visual acuity and contrast sensitivity in patients with amblyopia, mainly in the amblyopic eye, and some increase in contrast vision was reported also in the better eye (Porciatti et al., 1998). The long term effect

improvement lasted till 6 months and no side effects were reported and a suggested regime has been to prescribe treatment twice a year (Campos and Fresina, 2006).

Oral citicoline has been tried in amblyopic children in conjunction with occlusion and the results showed that although citicoline with patching was not more effective than patching alone, it seemed to stabilize the results for longer (Fresina et al., 2008).

In view of the findings of citicoline effects on retinal and optic nerve function in glaucoma and visual cortical function in amblyopia, we have examined the effects of citicoline on visual acuity and contrast vision in children with severe visual handicap.

3 VISUAL FUNCTIONS AND TESTING

3.1 VISUAL ACUITY

Visual acuity is a measure of the spatial resolution of the visual processing system and is usually tested with black objects and symbols on a white background for maximum contrast. Visual acuity is specified in terms of the visual angle subtended by finest spatial detail detected.

There are generally considered to be three types of visual acuity measures: detection acuity, resolution acuity, and identification/recognition acuity.

Detection acuity implies that the stimulus should be detected or distinguished from the background. In young children this function can be assessed with the Stycar rolling balls. In measuring the visual acuity the size of the object and the distance should be used.

In resolution acuity, the stimulus pattern is usually a black and white grating and this function can be tested by various preferential looking tests which is based on the fact that the child will look at the pattern. Grating acuity is reported in cycles/degree.

In recognition acuity the stimulus, a letter, symbol or number, should be recognized by the subject and /or identified by matching or naming. In visual acuity testing the minimal angle of resolution is estimated in minutes of an arc (Rydberg, 1998).

There are many types of visual acuity charts. The first was presented in 1862 by Hermann Snellen. He defined "standard vision" as the ability to recognize an optotype, a letter, with a bar width of 1 minute of arc. The optotypes in most visual acuity charts have the overall size that is five times that of the width of the optotype bar (Sloan, 1951).

Subsequently many different visual acuity charts have been designed, all based on the same principle, with letters or other symbols. The visual acuity measure is the minimal angle of resolution in relation to normal acuity. It can be expressed in decimals or fractions of normal acuity.
Louise Sloan (1959) presented a new optotype set of 10 letters, all to be shown in each line tested, in order to avoid the problem that not all letters are equally recognizable.

The larger letter sizes thus required more than one physical line. The Sloan test is presented at a distance of 20 feet or 6 m (Sloan, 1959).

Lea Hyvärinen created a chart, using figures (an apple, a house, a circle and a square) and arabic numbers (0 – 9) to measure visual acuity in preschool children. If the child could not name the optotype, he/she could indicate it by pointing to it on a matching chart with the symbols in front of him/her. The Lea tests are designed for testing at a distance (3 m) or near (40 cm) (Hyvärinen, 1998).

3.2   CONTRAST SENSITIVITY

Contrast is defined as the luminosity difference between object and surround. It is expressed in percent of the luminosity of the surround. Contrast sensitivity defines the lowest contrast level at which an object can be detected for a given size target. Normally a range of various target sizes are used in testing contrast sensitivity. Therefore contrast sensitivity measurements include two variables, size and contrast, while acuity measures represent size at a fixed contrast. Contrast sensitivity is measured clinically either with a set of charts consisting of bars with sinusoidal luminosity profile at varying bar width and contrast levels, or charts consisting of optotypes of varying size with square wave luminosity profile and varying contrast. Contrast sensitivity is expressed as a function of sensitivity against pattern size (Regan and Neima1983).

Among the tests available, the Vistech chart uses grating patterns, whereas most other charts e.g. Pelli-Robson and LH use optotype sets (Hyvärinen et al., 1990, Regan and Neima, 1983, Ferris et al., 1982).

Contrast sensitivity testing has proved useful in early diagnosis of retinal disorders, including diabetic retinopathy, age-related macular degeneration, and a variety of other retinal disorders. Additionally, measurement of the contrast sensitivity function has also been reported to be effective in revealing subtle visual losses in optic neuritis and multiple sclerosis, other optic neuropathies and amblyopia,

In addition to providing useful information about the functional integrity of the visual pathways, there is also evidence that the contrast sensitivity testing of low vision patients may be helpful in predicting the performance of various "real world" tasks,

such as recognition of obstacles in dim light, reading ability, face recognition, and orientation and mobility skills (Hyvärinen and Jacob, 2011).

3.3 FUNCTIONAL VISION

Interest in and need for functional correlates of visual measurement were first stimulated at the national level by development of the legal concept of indemnification, or liability, in Germany and Great Britain in the late 19th century. This development was spurred by industrialization and its resulting disabling accidents. The concept was brought to focus by Hugo Magnus, a one-time professor of ophthalmology in Germany, in a book on "visual economics" first published in German in 1894, and translated, with revisions, into English in 1902 (Ryan, 1962).

The full early history of attempts to quantify the functional implications of visual impairment, typically again for disability compensation purposes, is well reviewed elsewhere (Ryan, 1962). Various functional assessment testing algorithms are available with Jill Keefe's book for assessment in developing countries approved by the WHO and the VFQ 25 supported by the National Eye Institute (Keefe ,1995); NEI-VFQ-2000).

More recently Lea Hyvärinen presented a simple method of assessing the functional level of vision in school children. Functional vision was evaluated in five areas: communication, orientation, mobility, activities of daily life, sustained near vision tasks. This method was found to be easy to learn and repeat. The assessment of functional vision has not previously been compared with visual acuity and contrast sensitivity in a group of visually impaired children (Siddiqui et al., 2005).

4 AIMS AND OBJECTIVES OF THE STUDY

The aims have been to study in children with visual impairment

- correlation between the results of high contrast and low contrast visual acuity tests   in low vision children
- correlation between the contrast tests and functional visual assessment in low vision children
- differences in such testing with regard to peripheral and central visual dysfunction in low vision children
- effects of Citicoline treatment on contrast vision, also with regard to peripheral and central visual impairment in low vision children

5   MATERIALS AND METHODS:

5.1   PAPER I

Twenty children aged 6-16 years from the Al-Maktoom school for visually impaired children in Islamabad, Pakistan were included. Eleven of the children were girls and 9 boys.

The children were examined clinically for visual acuity, ocular motility status, anterior segment bio microscopy, fundus examination and refraction.

The children were divided into two groups:

1. The visual dysfunction was regarded as central (vision deprivation amblyopia, VDA).

Nine children had been operated late for congenital cataract and suffered vision deprivation.

2. The visual dysfunction was regarded as mainly peripheral (peripheral visual impairment, PVI).

Eleven children had retinal or optic nerve related diagnoses such as albinism, rod/cone dystrophy, retinal degeneration and primary optic atrophy. All children except three in the group with peripheral visual impairment showed nystagmus of the sensory type as a result of the early onset of severe visual impairment.

Both high and low contrast visual acuity was assessed, using cardboard letter charts. Previous studies in children with visual handicap had shown that visual function assessment with these tests corresponded quite well with assessment of the functional ability of the children (Siddiqui et al., 2005).

The distance visual acuity was assessed with the following high contrast distance tests at 90% contrast: Lea Symbol High Contrast test (Lshc), Lea Number High Contrast test (Lnhc) and Sloan Letter High Contrast tests (Slhc).

The distance low contrast tests presented at a contrast of 2.5 % were: Lea Symbol Low Contrast (Lslc), Lea Number Low Contrast (Lnlc) and Sloan Letter Low Contrast test (Sllc).

The near vision was tested with the near vision Lea Hyvärinen test (Nvlh) for a distance of 40 cm.

The visual acuity was recorded as the last line on which at least 3 out of 5 symbols were identified correctly except when the line was read twice, in that case 4 out of 5 were acceptable (Precision Vision TM, testing instructions). Visual acuity was recorded using the decimal notation. If not even the largest optotypes were identified, this was marked as "no response" and given an arbitrary acuity value of 0.01 in the statistical analysis.

Functional vision was evaluated in five areas:

Communication (use of facial expressions, visual initiation of communication).

Orientation (awareness of the surroundings at different levels of light).

Mobility (control of posture and body movements and ability to move in the environment)

Activities of daily life (participation in activities at school and home, performance in games).

Sustained Near vision tasks (performance with pictures and text, fixation pattern, need for optical devices).

The performance in the tasks were graded by the low vision teachers from 1 to 5 wherein

 1= blind behaviour and 5= sighted behaviour. For each child a total score of all test areas was calculated.

The Student´s t-test was used to compare visual acuity values between the two groups. Pearson´s correlation coefficient was used to compare high-contrast acuity, low-contrast acuity and functional vision scores.

5.2   PAPER II

A second group consisted of twenty-two children, age range 6 -14 years, with severe visual impairment, students the Al Maktoom School for the Visually Impaired. None of the children participated in the previous study of Paper I.

One group of 11 children had been operated late for congenital cataract, resulting in vision deprivation amblyopia (VDA).

Another group of 11 children presented with retinal or optic nerve disease and peripheral visual impairment (PVI).

All children received an intramuscular injection of 1 g of citicoline for 10 consecutive days.

Both high contrast and low contrast visual acuity was tested with methods described earlier. Acuity was measured at baseline (day 1), on day 30 and on day 90. Such studies have not been performed in children with severe visual impairment and treatment effects of citicoline have not been examined.

The visual acuity effects were also evaluated as the change from the baseline examination in the number of lines identified on the acuity chart. An improvement or a decline of two to three lines was considered a moderate effect, and a change of four lines or more as a marked effect.

The subjective changes of visual function were evaluated with the following questions put to the child at the examination on day 30 and 90:

Do you notice any brightening or darkening of light around you?

Do you think that the colours around you appear brighter/clearer or darker?

On the visual acuity data an ANOVA for repeated measures analysis was performed. The data were further examined for trends with a linear contrast analysis. All analyses were done with the STATISTICA, version 7.

6 RESULTS

6.1 PAPER I

The results of the examination of visual function for the different optotypes and
contrast tests are shown in Table 1A for the group with visual deprivation amblyopia
(VDA) and Table 1B for the group with peripheral visual impairment (PVI). The mean
values and standard deviations are presented. The values are expressed as Snellen
visual acuity in the decimal notation with Log MAR in parenthesis.

Table 1A. Results of testing of near and distance contrast vision in nine children with
Vision deprivation amblyopia (VDA). Mean values and standard deviation in Snellens decimal.

Tests	Nvlh	Lshc	Lnhc	Slhc	Lslc	Lnlc	Sllc
Contrast	high	high	high	high	low	low	low
Mean	0.12	0.16	0.134	0.133	0.059	0.051	0.043
Std Dev	0.09	0.074	0.087	0.056	0.037	0.035	0.035

Table 1B. Results of testing of near and distance contrast vision in eleven children with
Peripheral visual impairment (PVI). Mean values and standard deviation in Snellens decimal.

Tests	Nvlh	Lshc	Lnhc	Slhc	Lslc	Lnlc	Sllc
Contrast	high	high	high	high	low	low	low
Mean	0.065	0.101	0.081	0.076	0.044	0.036	0.032
Std Dev	0.040	0.041	0.040	0.034	0.034	0.033	0.023

A reduction of the contrast resulted in a decrease in visual acuity in the visually
impaired children of both groups. The acuities in children with VDA were higher than
in those with PVI and a significant difference between the two groups was found for
Lshc and Slhc.

Comparison of different contrast tests showed that high contrast tests were not
correlated amongst themselves or to low contrast tests. In contrast low contrast tests
showed good correlation amongst themselves and seem to be more reliable for contrast
vision assessments of visually impaired children. Looking at the correlation of all tests
irrespective of the group reveals the results as if they were an admixture of correlations
of both groups. Nvlh was significantly correlated with two low contrast tests; Lshc was
significantly correlated with all the tests except Lslc; Lnhc was only correlated with

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Slhc; and low contrast tests were all very well correlated amongst themselves, whereas the near vision and low contrast tests were better correlated in the VDA group than in the PVI group.The low contrast tests were well correlated amongst themselves in the VDA group.

The mean score of the functional assessment is shown in table 2A for visual deprivation amblyopia (VDA) and in table 2 B for peripheral visual impairment (PVI). The value for the central impairment group was nearly equal to the normally sighted with a mean of 23.44 in the total score. In the peripheral group, however scores were reduced for all the fields of assessment with a mean of 18.47.

Table 2A. Scores for functional assessment in eleven children with vision deprivation amblyopia (VDA). Mean values.

	Communication	Orient	Mob	ADL	Snvt	Total
Mean	4.66	4.77	4.88	4.88	4.22	23.44

Table 2B. Scores for functional assessment in nine children with peripheral visual impairment (PVI). Mean values.

	Communication	Orient	Mob	ADL	Snvt	Total
Mean	3.81	3.91	3.63	3.91	2.55	18.27

In children with peripheral visual impairment correlations existed with most of the low contrast tests and all the functional abilities except mobility. Due to little or no variation in the functional assessment of children in the central group, assessment of correlations to contrast test values could not be performed.

6.2   PAPER II

All children but two, both in the group with peripheral visual impairment reported subjective increase in brightness and colour during and up to 30 days after the citicoline treatment.

The baseline values of visual acuity at high- and low-contrast levels were not statistically different between the two groups. The over-all effect of citicoline treatment was an increase in visual acuity over time in both groups, but the change from baseline was not statistically significant. At 30 days after treatment start visual acuity had increased in the group with central impairment and it remained at this value in some children but decreased in others at the 60 days and 90 days test. In the group with peripheral impairment the effects were more varied, but an increase in low-contrast values were more common than in high-contrast testing. The statistical analysis showed a close to significant increase in visual acuity in the group with peripheral impairment but not in the group with central impairment.
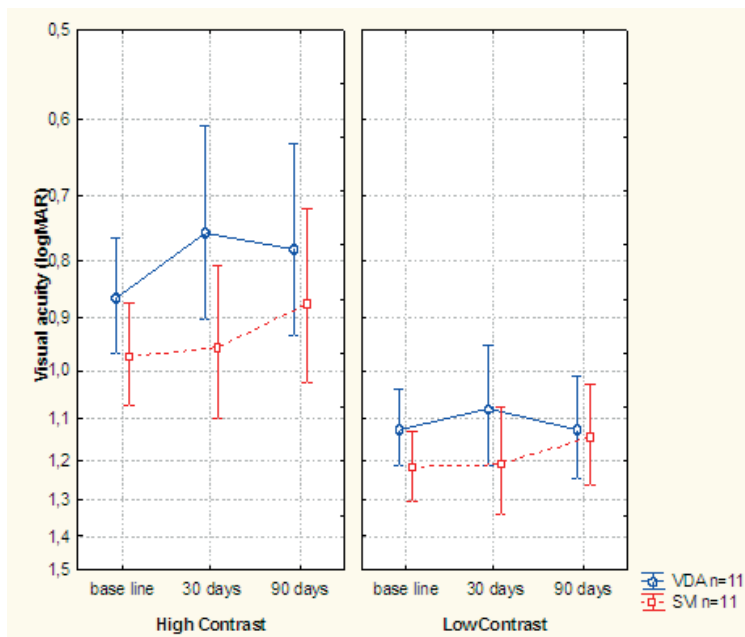
Figure 1. *Mean values in visual acuity for the HCA and for LCA*

The clinical assessment of visual acuity change, evaluated as the change in the number of lines seen on the chart, showed a moderate and marked improvement of high-contrast vision in 6/11 children with central visual impairment and in 3/11 children with peripheral visual impairment. Low-contrast vision was improved in 3/11 children with central impairment but only in one child with peripheral impairment. The improvement in children with central visual deprivation was seen mainly during the period up to 30 days after citicoline treatment, while the improvement in the children with peripheral visual impairment occurred during a longer period, up to 90 days. A

decline in acuity after treatment was observed in 2/11 children with VDA and 3/11 children with PVI.

7   DISCUSSION

7.1   GROUPING OF THE STUDY POPULATION

At the very outset of testing it was noticed that the children had two distinct aetiological diagnoses. (Siddiqui et al., 2005). It appeared logical at that stage to group them accordingly.

We grouped the children with history of delayed surgery for congenital cataracts, corneal opacities and other media opacities into "Vision Deprivation Amblyopia" (VDA). The commonality being the hindrance to visual stimulation due to anterior segment related causation.

In children with infantile cataracts, the timing of the surgery and its relation to the duration of deprivation, accurate optical rehabilitation and post-operative supervision are essential. Cataract surgery amongst infants should generally be done within 6-10 weeks of birth (Lloyd et al 2007), and surgery delayed beyond this very short period would lead to visual acuity not improving beyond 6/60 or 1.0 (LogMAR) [0.1 in decimal Snellen and 20/200 when converting to feet] even after the most aggressive optical rehabilitation (Ruth and Lambert, 2006).

In most of our children the surgery was not done till they were 8 years or above, therefore the chance of any optical correction leading to improvement of vision was far gone. For some of them the surgery was done within a few years of birth the optical rehabilitation was not optimal.

The children whose basic cause of visual impairment were from causes related to affecting the first order neurons and beyond i.e, optic atrophy, macular hypoplasia and other retino-optic causes were grouped into the "Peripheral Visual Impairment group"(PVI) (Siddiqui et al, 2005).

7.2   VISION TESTING METHODS

All the children were tested with the same tests in high and low contrast card board based tests using various symbols, (Siddiqui et al., 2005). In clinical settings only a few tests are available to assess low contrast acuity in children (Rydberg et al., 1997).

Low contrast tests based on gratings are usually thought of being time consuming and more difficult to understand for most subjects especially children and, therefore, we have used card board based tests which have the same symbols as the high contrast tests so that it would be more convenient for children to respond also bearing in mind these children were all visually impaired. Visual information at low contrast levels is important in communication and orientation and mobility but also in seeing black-and-white photographs and pastel colour paintings and pictures. Contrast sensitivity is decreased in many diseases. Corneal opacities, cataract, optic nerve atrophy and retinal degenerations are the most common (Hyvärinen, 1997)

In the 1980's Regan and Neima, Pelli and Robson, Hyvärinen, and various practitioners came up with their versions of chart based Low contrast tests which brought the testing of low contrast from the laboratory into the clinic (Pelli et al., 1988, Hyvärinen et al., 1990, Regan and Neima, 1983)

In particular, the charts picked up visual loss that was not detected by the standard Snellen chart: they detected visual pathway dysfunction in all seven patients whose sinewave data were abnormal (Regan and Neima, 1983)

On average, a four-line (0.4 logMAR) reduction in acuity should be expected when one is comparing high-contrast acuity with a 2.5% low-contrast acuity measurement using Lea symbols (Little et al.,2013).

This is further confirmed by Lea Hyvärinen who states that in groups of visually normal children, the mean value of low contrast visual acuity values is slightly less than half of the full contrast visual acuity value (Lea test webpage).

In this study the low contrast acuities were less than half of the high contrast acuities for all of the test charts used (Table 1 A and B).

The visual acuity was generally higher both for high- and low-contrast testing in the children with visual deprivation than in the children with retinal and optic nerve disease (Paper I).

As pointed out by Lewis and Maurer, patterned visual input immediately after birth plays a vital role in the construction and preservation of the neural architecture that later

on mediates higher and lower aspects of vision. Both systems of development of fine acuity and low contrast acuity are refined by later visual experience which is present in children with congenital cataracts whereas the children with retino-optic and macular lesions would not have the possibility of such stimuli (Lewis and Maurer, 2009).

It was seen that the High contrast tests did not correlate well among themselves or to low contrast tests, whereas the low contrast tests correlated well among themselves and seem to be more reliable for contrast assessments of visually impaired children.

7.3 FUNCTIONAL ASSESSMENT

Functional assessment seems to be a more holistic way of assessing children so that their needs can be looked in more detail. It also helps us in making a more well-rounded picture of the child. It was encouraging to note that the children mostly were well adjusted in spite of their impairment. (Paper 1)

Jill Keefe designed a detailed functional assessment booklet to be used in the developing countries and is approved by the WHO (Keefe 1995). It was found to be rather detailed and time consuming and required quite a bit of training for the teachers.

The National Eye Institute VFQ-25 is another well accepted but very detailed method used to quantify Functional vision (NEI-VFQ,2000).

The Functional assessment protocol used in our studies was the simplest and most easily taught method and it has been tried and tested in children in a different countries of the world (Hyvärinen, 1998).

We used four different tasks to be assessed i.e. Communication, orientation and mobility, activities of daily living and sustained near vision tasks and then graded them from 1-5 (Hyvärinen, 1998).
Functional vision was almost normal for children with visual deprivation but not in the children with retinal or optic nerve involvement. The results of functional assessment were well correlated with low-contrast visual acuity in the children with retinal/optic nerve disease, therefore better at assessing communication and orientation and mobility tasks but lacking in assessing activities of daily living and sustained near vision tasks, i.e. reading. Increase in contrast in the later tasks would be beneficial for the children.

For a broad evaluation of the visual capabilities of children with impaired vision it is suggested that the visual examination should include both high- and low-contrast tests and functional vision assessment (Siddiqui et al., 2005).

7.4   PHARMACOLOGICAL TREATMENT

Over the last few years studies have been carried out to look into pharmacological treatment of amblyopia by medicines which were previously being used for different conditions for example levodopa and citicoline (Gottlob and Stangler-Zuschrott, 1990; Leguire et al., 1993; Campos et al., 1995; Porciatti et al., 1998).

We have broadened the scope of citicoline use to included children with visual impairment due to visual deprivation or to retino-optic causes. An increase in visual acuity, measured with high and low contrast tests were observed in both groups but the effect was not statistically significant. The change in visual acuity, based upon grouping on the basis of aetiological diagnoses have shown different results in both groups. The children in the VDA group, showed an improvement in the first 30 days of treatment whereas, the children in the PVI group showed more improvement between day 30 and 90. A more qualitative assessment of visual acuity, measured as the number of lines of improvement or decline on the acuity chart, also showed that citicoline improved vision, more in the children with visual deprivation than in children with retinal/optic nerve involvement.

Most of the change did regress to baseline at the end of 4 months, which corresponds to the effects reported in patients with amblyopia (Parisi et a., 1999, Fresina et al., 2008, Campos et al., 1995; 1997).

Citicoline seems to be safe when taken up to 90 days, and long term side effects are rare i.e., insomnia, headache, nausea, diarrhoea, blurred vision and low or high blood pressure.
(http://www.webmd.com/vitamins-supplements/ingredientmono-1090-CITICOLINE.aspx)

The results of this pilot study on citicoline effects are encouraging but extended examinations are needed to determine treatment procedures for citicoline treatment of visual dysfunction in children with severe visual impairment.

8 ACKNOWLEDGEMENTS

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