Ocular Manifestations in Neurocutaneous Syndromes with Emphasis on Neurofibromatosis – A Descriptive Observational Study

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ABSTRACT

BACKGROUND

Neurocutaneous syndromes (NCS) are a group of genetic disorders that produce a variety of developmental abnormalities of the eye. Ophthalmic manifestations usually appear early in life and progress with time. The study was conducted to know the prevalence of ocular manifestations in neurocutaneous syndromes with emphasis on neurofibromatosis.

METHODS

This study was conducted in ophthalmology department at a tertiary care hospital during a period of 2 years among 30 patients. All phakomatoses referred from other specialty departments for ophthalmological evaluation and cases diagnosed in ophthalmology department during routine evaluation were included in the study.

RESULTS

Neurofibromatosis type 1 (NF-1) accounted for most of (66.67 %) the cases followed by Sturge Weber syndrome (SWS) (20 %). Majority (55 %) of NF-1 and 83.33 % of SWS and all patients of other phakomatoses were in the age group < 30 yrs. 55 % of NF-1 patients were males. 65 % of NF-1 patients gave positive family history. Lisch nodules, the most common ocular finding in NF-1 were present in 85 % of patients and of these 82 % were bilateral. Medullated nerve fibre was seen in 10 % of patients. Glaucoma was seen in 66.67 % of Sturge Weber syndrome patients. Conjunctional telangiectasia was seen in 16.67 % of Sturge Weber syndrome patients. Seizures and radiological features were seen in most patients with Sturge Weber syndrome. Megalocornea with normal intraocular pressure (IOP) was seen in both of our patients with posterior fossa malformations, haemangioma, arterial anomalies, coarctation of the aorta/cardiac defects, and eye abnormalities (PHACES syndrome). Eyelid coloboma, ectropion uvea, hyperchromia iridis & myopia was seen in one patient with PHACES syndrome. A case of tuberous sclerosis had many systemic features like calcified subependymal nodules, renal angiomyolipomas, skin features and the only ocular finding was hypopigmented iris spots.

CONCLUSIONS

Ophthalmologist has a role in early recognition of the neurocutaneous syndrome from specific ocular features (like Lisch nodule in NF-1), reducing ocular morbidity by timely treatment (of conditions like glaucoma) and prompt referral to concerned speciality for management of systemic involvement.

KEYWORDS

Neurofibromatosis, Sturge Weber Syndrome, Tuberous Sclerosis

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BACKGROUND

Phakomatosis is a group of hereditary disorders characterised by hamartomas of the skin, eye, CNS and other viscera derived from all three embryonic layers.[1] The management of these condition involves a multidisciplinary approach. Four classical syndromes included in phakomatosis are:

1. Neurofibromatosis 1 (Von Recklinghausen disease) & Neurofibromatosis 11.
2. Tuberous sclerosis (Bourneville disease).
3. Angiomatosis retinae (Von-Hippel-Lindau disease).
4. Encephalo facial angiomatosis (Sturge weber syndrome).

Other phakomatoses or neurocutaneous syndromes include, ataxia telangiectasia (Louis-Bar syndrome), hypomelanosis of Ito (incontinentia pigmenti), xeroderma pigmentosum, Cockayne syndrome, Gorlin syndrome, Wyburn Mason syndrome, PHACES syndrome, Klippel-Trenaunay-Weber syndrome.

Neurofibromatosis 1 (NF1) was first described by Von Recklinghausen and it is the peripheral form of the disease. NF1 is an autosomal dominant condition with the NF1 gene being localised to the long arm of chromosome 17. The abnormality leads to decreased production of the tumour suppressor protein neurofibromin, which results in the generalised multisystem manifestations of the disease. Ocular findings in neurofibromatosis from anterior to posterior include the classical plexiform eyelid neurofibroma, simple neurofibromas over the eyelid and face, prominent corneal nerves, Lisch nodules, ectropion uvea, glaucoma (the risk is higher with ipsilateral hemihypertrophy of the face), ectropion uveae, pulsatile proptosis due to sphenoid wing dysplasia, proptosis due to optic nerve gliomas and orbital schwannomas, choroidal nevi, epiretinal membranes, combined hamartomas of the retinal pigment epithelium (RPE) and retina, disk hamartomas, myelinated nerve fibers and glial tissue.[2]

NF2 is genetically and clinically distinct from NF1. It is characterised by the development of CNS tumours, notably bilateral vestibular schwannomas. The gene for NF2 has been mapped to the long arm of chromosome 22. Lisch nodules are rare. Posterior subcapsular cataract (85 %), central epiretinal membranes in the posterior pole & macula, combined pigment epithelial and retina hamartomas, optic nerve sheath meningioma are the other ocular findings.

Tuberous sclerosis is a protean disorder, chiefly manifested by mental deficiency, epilepsy and skin lesions. It is transmitted as an autosomal dominant gene. Ocular features specifically comprise hypopigmented spots in the iris, retinal phakoma, characterised by gray coloured mulberry like proliferation in the retina, retinal achromic patches, vascular sheathing and astrocytomas of the optic disc. There can be secondary retinal detachment and vitreous haemorrhage due to these retinal proliferations, which may require surgical interventions for rehabilitation.

The hallmark of Sturge Weber syndrome is leptomeningeal angiomatosis that involves one or more lobes in one or both hemispheres. A port-wine stain on the face is a relatively common malformation. Ophthalmic manifestations of the conditions include glaucoma, usually ipsilateral to the side of the nevus flammeus, which may present very early, even at birth, leading to buphthalmos and usually recalcitrant to conventional modes of therapy. Increased conjunctival vascularity, indicating episcleral haemangiomatous formations, resulting in increased episcleral pressures, may be present. Both increased episcleral venous pressure and developmental anomalies of the anterior chamber angle are postulated as possible causes of glaucoma in such patients. Retinal vascular tortuosity with arteriovenous communications may be present. Iris heterochromia, with the darker iris on the side of the nevus flammeus may be present. Other ocular features include choroidal haemangiomas and eyelid haemangiomas, which may result in mechanical ptosis.

As a rule, Von-Hippel-Lindau disease (VHL) disease do not present in children, although cerebellar haemangioblastomas can be seen as early as 9 years of age. More often symptoms are delayed until the second or third decade. They may be referred to ophthalmologist with sudden intraocular haemorrhage or to the posterior fossa with increased intracranial pressure or cerebellar signs. Ophthalmic manifestations include retinal capillary haemangioma characterised by reddish spherical lesion fed and drained by dilated tortuous retinal blood vessel.

Ataxia Telangiectasia is an autosomal recessive genetic disorder, localised to chromosome 11 q 22 characterised by oculocutaneous telangiectasia, progressive cerebellar ataxia and recurrent respiratory and sinus infections. Ocular manifestations of the condition include bulbar telangiectasia that usually appears after the onset of ataxia, at about five years of age. Oculomotor apraxia, abnormalities in saccadic initiation impaired convergence, nystagmus and loss of optokinetic nystagmus (OKN) response are some of the ophthalmic associations of the condition.

PHACES syndrome is characterised by posterior fossa abnormalities haemangiomas, arterial abnormalities of neck and brain, cardiac abnormalities, eye abnormalities and sternal abnormalities.

METHODS

Approval from the institutional ethical committee was obtained before starting the study. This descriptive observational study was conducted from 1st January 2008 to 31st January 2010 in ophthalmology department at a tertiary care hospital in Kerala during a period of 2 years.

All twenty-two phakomatoses cases referred from other specialty departments for ophthalmological evaluation and eight cases diagnosed in ophthalmology department during routine evaluation of unrelated ocular symptoms or presenting features like headache or glaucoma who satisfied diagnostic criteria of phakomatoses were included in the study. Neurofibromatosis type 1 (NF1) is the most common of all the neurocutaneous syndromes, with a prevalence of 1:3000 compared to neurofibromatosis type 2 (NF2) with a prevalence of 1:25,000. Tuberous sclerosis complex (TSC) has a prevalence of 1:6,000 individuals worldwide. Since

phacomatosis was a rare disease sample size was taken as 30 for statistical significance.

A general examination and systemic examination of central nervous system (CNS), skin, skeletal, endocrine, gastrointestinal tract (GIT), cardiovascular system (CVS) and respiratory system was done. Ocular examination included slit lamp examination, detailed fundus examination including indirect ophthalmoscopy if necessary and recording of vision, colour vision, fields, IOP and refraction. A gonioscopy was done to rule out angle anomalies. Radiological investigations included plain x-ray skull, computed tomography (CT) brain, magnetic resonance imaging (MRI) brain and whenever possible ultrasonography was also done in some cases.

Baseline data was entered in Microsoft Excel sheet. Data was analysed using Statistical Package for the Social Sciences (SPSS) trial version 20. Quantitative variables were analysed using mean and standard deviation and qualitative variables were analysed using percentages and proportions.

RESULTS

Condition	Number	%	Males	Females
NF-1	20	66.67	11 (55 %)	9 (45 %)
SWS	6	20	1 (20 %)	4 (80 %)
PHACES	2	6.7		2 (100 %)
TS	1	3.3		1 (100 %)
AT	1	3.3		1 (100 %)

Table 1. Distribution of Total Cases and Sex Distribution of Phacomatosis in Our Study

For sex distribution $X^2 = 1.96$, $p = 0.161$ (not significant)

Ocular	No of Patients with Defect / Total No. of NF-1 Patients
Lisch nodule	17 / 20
Upper lid neurofibroma	3 / 20
Plexiform neurofibroma	1 / 20
Prominent corneal nerves	3 / 20
Prominent iris process	5 / 20
Iris mamillations	3 / 20
Heterochromia iridis	1 / 20
Hyperpigmented iris spots	5 / 20
Posterior subcapsular cataract	5 / 20
Medullated nerve fibre	2 / 20
Papilloedema (obstructive hydrocephalus-aqueductal stenosis)	1 / 20
Skin dermal neurofibroma café au lait spots axillary freckling	20 / 20
Bone kyphosis scoliosis short stature	3 / 20
GIT neurofibrosarcoma abdomen with liver metastasis	2 / 20
CNS-low intelligence hyperactivity syndrome paraplegia	4 / 20

Table 2. Findings in Neurofibromatosis-1 in Our Study

Findings	Number	Total No. of Patients	Percentage
Glaucoma	4	6	66.67 %
Megalocornea	2	6	33.33 %
Port-wine stain over face	6	6	100 %
Prominent episcleral vessels	1	6	16.67 %
Blood in schlemm's canal	2	6	33.37 %
Blue sclera	1	6	16.67 %
Glaucomatous optic neuropathy	4	6	66.67 %
Right homonymous quadrantanopia	1	6	16.67 %
Low intelligence	1	6	16.67 %
Intracranial calcification	5	6	83.33 %

Table 3. Sturge Weber Syndrome – Findings and Distribution in Our Study

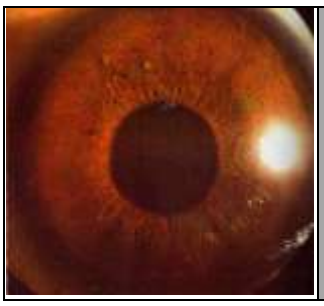

Figure 1. Lisch Nodule

Figure 2. SWS with Port-Wine Stain in the Distribution of First Division of Trigeminal Nerve

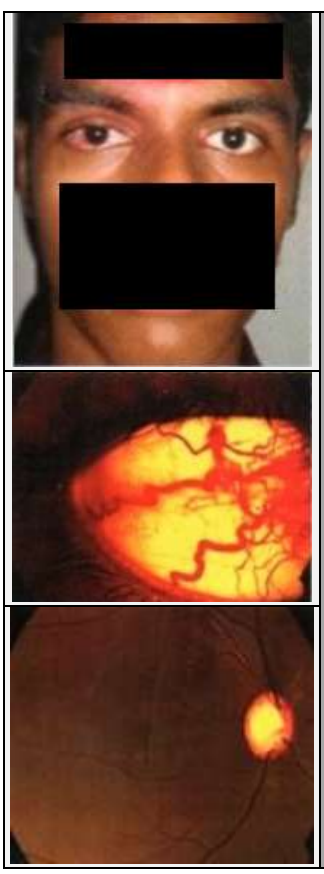

Figure 3. SWS with Port-Wine Stain on Right Side with Conjunctival Angiomas and Glaucomatous Optic Neuropathy

Figure 4. Ataxia Telangiectasia with Conjunctival Telangiectasia and Oculomotor Apraxia

NF-1 accounted for most of (66.67 %) the cases followed by Sturge Weber syndrome (20 %). Majority (55 %) of NF-1 and 83.33 % of SWS and all patients of other phakomatoses were in the age group < 30 yrs. 55 % of NF-

1 patients were males. 65 % of NF-1 patients gave positive family history. Lisch nodules, the most common ocular finding in NF-1 were present in 85 % of patients and of these 82 % were bilateral. Enlarged corneal nerves were seen in 15 % patient. Glaucoma was seen in 66.67 % of Sturge Weber syndrome patients. Conjunctional telangiectasia was seen in 16.67 % of Sturge Weber syndrome patients. Megalocornea with normal IOP was seen in both of our patients with PHACES syndrome. A case of tuberous sclerosis had many systemic features like calcified subependymal nodules, renal angiomyolipomas, skin features and the only ocular finding was hypopigmented iris spots.

DISCUSSION

A total of 30 cases of phakomatoses were studied of which majority were Neurofibromatosis-1 followed by Sturge Weber Syndrome. According to a study conducted by Riccardi V.M, 1992[3] also NF-1 is the most common phakomatoses and Tuberous sclerosis is the second most common phakomatoses but in the present study Sturge Weber Syndrome is the second most common phakomatoses. We didn't have NF 2 patients in our study. Majority of the phakomatoses were in the age group < 30 yrs. NF-1 had 55 % of patient in the age group < 30 yrs. whereas PHACES syndrome, Tuberous Sclerosis, Ataxia telangiectasia had all the patients in < 30 yrs. age group and Sturge Weber Syndrome had 83.33 % in the age group < 20 years Majority of Neurofibromatosis-1 patients were males (55 %) whereas Sturge Weber Syndrome had majority females (80 %). The observed differences were statistically not significant. PHACES Syndrome, Tuberous Sclerosis, Ataxia Telangiectasis had 100 % females. According to other studies NF-1 has equal male: female ratio & PHACES syndrome is seen exclusively in females.[4]

In our study we had 65 % of patients with a positive family history of neurofibromatosis. None of the other syndrome had a positive family history. Lisch nodules are the commonest ophthalmic manifestation of NF-1.[5] The prevalence of Lisch nodule was greater than that of neurofibromas in all, but the youngest age group. Boltshauser, 1985 reported that Lisch nodule are found in 5 % of NF-1 patients less than 3 yrs. contrary to the previous belief that they do not appear until the age of 16 yrs.[6] In the present study, we had only one child < 3 yr. who did not have Lisch nodules. The incidence of Lisch nodule as reported in various series ranges from 30 to 97 %. In this study 85 % of patients had Lisch nodules which is comparable with the previous report and the youngest patient with Lisch nodule was of 5 years age.

Lisch nodules are histologically melanocytic hamartomas containing various amount of pigments and therefore are presumed to be of to be neural crest origin embryologically. Rajesh et al, 1991 studies showed Lisch nodules were bilateral in 95 %.[7] In our study we found Lisch Nodules bilaterally in 82.35 % of the patients. In the study 17.65 % patients had unilateral Lisch nodules and all these belong to < 30 yrs. age group. Single Lisch nodules was noted in 75 % of patients and these were aged < 10 yrs. All adult patients (70 %) had multiple Lisch nodules.

All patients above 30 years had bilateral Lisch nodules. Another interesting finding is that 100 % of female's patients has Lisch nodules while only 72.7 % of males had Lisch nodules.

Neurofibromas involving the upper eyelid is diagnostically very suggestive picture of NF-1 its incidence is 15 % (3 / 20) in this present study. Obstructive hydrocephalus with papilloedema was found in one patient. In our study medullated nerve fibre was seen in 10 % (2 / 20) and prominent corneal nerves in 15 % (3 / 20) of patients. The absence of choroidal hamartoma and glaucoma in this report is striking.

In our patients with NF 1, prominent iris processes were identified in 5 patients, but none of them had glaucoma. This may be attributed to the comparatively less number of patients comprising this study.

In a series of Holt, optic nerve gliomas were found in 23 % of children with NF-1.[8] Approximately 10 - 20 % of gliomas in the optic Nerve and optic chiasma are known to be associated with NF-1. The small size of the sample also explains the absence of optic pathway gliomas in our study.

In one patient MRI spine showed two neurofibromas in the upper cervical region compressing the spinal cord and another patient has neurofibrosarcoma with metastasis in the liver and obstructive hydrocephalus.

Out of the 6 Sturge Weber patients four (66.67 %) had glaucoma. One patient had congenital glaucoma and three had early onset primary open angle glaucoma. Three of the patients experienced onset after 16 years of age while one child had it before 2 years of age. Glaucoma is of the infantile type in 70 % and adult type without enlargement of globe in 30 % and may occur at any age.[9]

The glaucoma as a rule is unilateral. Sullivan et al reported 71 % of Sturge Weber Syndrome with glaucoma.[10] All of them had port wine stain involving the upper eyelid. Of the 2 patients who did not have glaucoma one had Port wine stain sparing the upper eyelid. Port wine stain in many patients showed minor transmedian involvement. Prominent episcleral venous plexus was seen in only 16. 67 % in our study. Stores Jack reported incidence of episcleral telangiectasia in 70 % of patients and iris heterochromia in 10 %. Gonioscopy showed blood in Schemm's canal in two patients. No other angle anomaly was detected. Fundus examination of the glaucoma patients showed typical glaucomatous changes like increased cupping, baring of circumlinear vessels, bayonetting and peripapillary RNFL changes. Diffuse choroidal angioma are the most common type. They are flat lesions that involve the entire posterior pole "tomato catsup fundus". Diffuse red velvet texture that lacks normal choroidal marks. Localized angiomas are less common, but are associated with secondary serous detachment of the retina. In our study no patient had choroidal haemangiomas.

Among the systemic manifestations four patients had intracranial calcification and one patient had curvilinear hyperdensity over left parietooccipital region who demonstrated right quadrantanopia.

Ocular abnormalities are seen in 20 % of patients with PHACES syndrome[11] (Adams 2009). Eyelid coloboma, megalocornea, hyperchromia iridis, ectropion uvea, myopia, facial haemangiomas, mucosal haemangiomas and cardiac defect were the findings in our cases. In 70 % cases only one extracutaneous manifestation is present. In both of our children haemangiomas involving upper part of face, cardiovascular system and eye was affected. It has been suggested that haemangiomas in upper half of face had greater risk for associated structural brain, cerebrovascular and ocular anomalies. The common manifestation was megalocornea, the IOP being normal. Iris abnormalities like ectropion uvea, heterochromia iris were seen in one patient and the other child had no other ocular abnormality except for megalocornea.

Ocular finding of significance in our tuberous sclerosis patients is only hypochromic iris and retinal lattice degeneration. Iris abnormalities though rare reported are focal areas of stromal depigmentation & atypical coloboma. According to Klin Oczna 1994 retinal tumours are found in 19 % of patients. The tuberous sclerosis patients usually (4 - 53 %) do not have any ocular complaints because the retinal astrocytoma which is the most common retinal tumours do not produce much symptoms. Our patient had cutaneous & visceral findings definitive of tuberous sclerosis adenoma sebaceum, shageen patch. ungual tumour, B / L renal angiomyolipoma calcified subependymal nodules. Nearly 50 % of individuals with TS have eye involvement & 50 % of it is unilateral.[12]

A single case of Ataxia Telangiectasia was there in our study who had ocular motor apraxia, conjunctival telangiectasia BE, ataxia, bronchiectasis, cerebral atrophy and mental retardation. Arman et al, 2002 had reported that Conjunctival telangiectasia is present in 91 % of patients and skin telangiectasia in 33 % of patients.[13] Other important ocular finding are strabismus (38 %) and ocular motor apraxia (30 %). Affected individuals of this condition develop progressive cerebellar ataxia, ocular cutaneous telangiectasia, radio sensitivity, predisposition to lymphoid malignancy and immunodeficiency.

CONCLUSIONS

Phakomatoses in general are characterised by hereditary transmission, multisystem involvement, slow evolution of lesion in childhood and adolescence, tendency to form hamartomas and a disposition to malignant transformation. So, the management of condition involves a multi-disciplinary approach. Since these conditions are hereditary, a pedigree analysis of the family and karyotyping (if facilities are available) should be done and genetic counseling offered to the parent or proband. Prenatal diagnosis also has a role in certain disorders. Ophthalmologist has a role in early recognition of the neurocutaneous syndrome from specific ocular features (like Lisch nodule in NF-1), in reducing ocular morbidity by timely treatment (of conditions like glaucoma) and prompt referral to appropriate specialities for management of complications involving other systems. This measure can at times be lifesaving as phakomatoses are often associated with intracranial neoplasms and their malignancies. Considering the slow evolution of lesions in phakomatoses and latency before the onset of symptoms, radiological investigations like USG, CT and MRI done even in an asymptomatic patient will be useful in early detection of the pathology. It is also necessary to follow up these patients as many lesions can undergo malignant transformation in course of time. To conclude, by coordinated effort between ophthalmologists and other specialties, the morbidity and mortality of individuals affected by phakomatoses can be reduced and quality of life can be improved by proper rehabilitative measures.

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