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"CLINICAL STUDY OF RETINOBLASTOMA IN KHARTOUM EYE HOSPITAL"

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Dedicated to my father and my mother.
ACKNOWLEDGMENTS
OBJECTIVES
Objectives

1- To review the distribution of affected patients with retinoblastoma by age and sex.

2- To investigate the regional and tribal distribution of the patients with retinoblastoma.

3- To see the effect of parental consanguinity in development of retinoblastoma.

4- To study the socio-economic status of patients with retinoblastoma.

5- To see the effect of heredity and teratogens in development of retinoblastoma.

6- To study the time and node of presentation of retinoblastoma in Khartoum eye hospital.

7- To study the clinical picture and the course of the disease.

8- To assess the value of treatment in these patients.
Abstract

Thirty six unselected patients with retinoblastoma presented to the eye hospital. Full history was taken, investigations were done e.g X-rays. Management of these patients was done.

Regarding the age of these patients, it was found that, the age of the patients at time of diagnosis was between 6 month and 3 years, and about 19 patients from one to three years. It was found that the two sexes were equally affected (19 females and 17 males).

From this study about 19 patients (52.7%) came from the western Sudan, Kordofán and Darfur. And about the tribal distribution it was found that 3 tribes shared high percentage, these are the Shua, Fur and Galyeen tribes.

Also this study indicated that high percentage of positive parental consanguinity (86.1%) among the parents of the affected children. The most of this is first degree relationship (72.2%). The time of the onset was between one year and three years old. Also we reached a conclusion indicated that there was delay between time of onset and time of presentation to the hospital.

Regarding the eye or both eyes involved, it was found that (77.5%) of the patients presented with bilateral retinoblastoma, this percentage goes normal with other series which reported from 30-40%. The presenting symptoms and signs in these patients, about 17 patients (47.5%) presented with ocular mass, where 11 patients about (30.5%) were presented by leukocoria. This was due to delay of presentation to the hospital because of the transport problem and other factors.

Radiological picture for many reasons not indicated any calcification.

Due to the delay in presentation to the hospital, most of the patients came with advanced course of retinoblastoma. Enucleation was done for most of these patients, some parents refused the operation, so presented latter with advanced course.
INTRODUCTION
"Encephaloid cancer" (Waldeyer 1853) was termed glioma oth retina, on the authority of the great pathologist of Berlin, even although it was entirely different both in type and happen from a glioma of the brain. The subsequent detailed studies of such investigators as J. Knapp (1868), Mieschberg (1866) - (1869) who introduced the classification of glioma exophytic and endophytic, Flexner (1881) and Wintersteiner (1897), however, defined the natural history and histology of these tumors and their metastases and established beyond question their non-sarcomatous nature and their neural origin. Simon Flexner indeed first describe the presence of rosettes in the tumor and suggested the name neuro-epithelial rosettes instead of glioma, but it was essentially to say that after studies of Wintersteiner the classical studies stopped and a modern work of retinoblastoma begins.

The embryonic nature of the cells had been stressed by Callins (1896) a view elaborated by Ginsberg (1899 - 1901) who considered that there had not yet developed but could potentially from spongioblastas (glial cells) and neuroblasts (nerve cells), the rosettes within the tumor developing from undifferntiated cells in their course of proliferation in a manner somewhat akin to the cylindrical cells of pars ciliaris retinae, at a considerably later date Fischer (1918) (10), in view of the embryonic character of the growth, proposed the term neuroblastoma, and Verhoeff (1913) retinoblastoma, which latter was adopted after considerable discussion as a general term by the American ophthalmological society in (1926) (10).

Incidence

Retinoblastomas is the most common intra-ocular tumor of childhood, occurring second in frequency to malignant melanoma. So retinoblastomas about 3% and malignant melanoma 4%. Nevertheless they are very rare forming 0.01% to 0.04% of all diseases of the eye.

Age

The age of incidence is limited almost exclusively to the early years of life, the tumor may attain a considerable size at birth or at age of 4 days, and often during the first month of life. The most frequent age diagnosis is 2 years, after age of 4 years becomes exceptional.

The age of onset is earlier in bilateral cases, in these dolyum and auver (1953) found an average of 1 year and 10 month compared with 3 years and 6 month in unilateral cases.

Sex

Has little bearing on the frequency, boys and girls more or less are equally affected.
NON-GENETIC RETINOBLASTOMA:

A non-genetic retinoblastoma is the result of a somatic mutation in the retina of the affected child. It has been suggested that the mutation arises in a single retinal cell. Non-heritable retinoblastomas, which cannot be transmitted, constitute a majority of all retinoblastomas, always appear sporadically and are almost certainly always unilateral.

Unfortunately, there is no present way of distinguishing them either clinically or pathologically from sporadically occurring unilateral genitic retinoblastomas.

Patients with retinoblastomas almost always have normal karyotypes, but a small number of children have been reported in whom there was a deletion of the long arm of chromosome 13, with or without translocation. And some of the children were mentally retarded. An association between retinoblastoma and Down syndrome has very occasionally been noted (Corver, pathology).

All bilateral cases can be considered to be mutation because of the proportion of the affected individuals among the off spring is near 50%, the expected incidence for an autosomal dominant disorder.

This can be applied to 35-50% of retinoblastomas. Using the same rationale for the etiology in the 10% of sporadic, unilaterally affected patients with affected offspring may conclude that 35-45% of retinoblastomas are heritable (7-10).

Mechanism of transmission:

Malignant transformation in retinoblastomas are largely unknown, but Kimer and others propose that ubiquitous virus present in genotypically susceptible retina may be primary mechanism of this malignant transformation (7-12).

CLINICAL COURSE:

Retinoblastoma occurs usually in young children in eyes that are otherwise normal, showing no deformity in the anterior segment the tumor to seen in any part of the retina and although the posterior area around the disc or macula is usually affected, the extreme periphery may seen as initial site. The tumor may be solitary, but a characteristic and common feature in the multiplicity of the growth up to ten or more of various sizes, these may be comprised of a large tumor surrounded by several small growths, a number of apparently independent masses of the whole retina may be sprinkled with neoplasms of various sizes, while similar growths, usually less numerous and marked, may be seen in the other eye. Some of these smaller tumors may be satellites from a parent neoplasm but in the majority of cases they are independent focus, an expression of the multigenic origin of the
The retina may be pressed forward behind and thus obscure a clear ophthalmoscopic view of the actual tumour. In the earlier stages it appears as an elevated grey zone. In later stages the retina shows a progressive detachment which eventually becomes total. With funnel shaped configuration, behind which one region as a rule is more translucent than the remainder. In these cases the presence of calcium deposits of chalk - white appearance can be decisive in the diagnosis (13).

Endophytum type:

Growth is directed into mainly the vitreous the retina remaining undetached. Groups of neoplastic cells migrate through the vitreous to other parts of the retina and even to the anterior segment. Seeding tumours may thus be established on the ciliary body, iris and corneal endothelium, and sediment of malignant cells may be deposited in the lower filtering space. Ophthalmoscopically the neoplastic tissue in the retina and anterior segment can be viewed directly.

Some retinoblastomas grow simultaneously outwards into the subretinal space and inward the vitreous and so exhibit the features of both types of growth. In either event, as the neoplasm grows larger it infiltrates and replaces the retina and overrules the secondary implants. Degeneration and atrophy of the intracellular structure ensues: the increasing volume of the intraocular mass may lead to the glaucoma, expansion of the globe, thinning of the corneoscleral envelope and the formation of staphyloma.

Elevated intraocular pressure is known to be associated with primary and metastatic ocular neoplasm. Various mechanisms including glaucoma have been seen in ocular melanoma, metastatic cinomas, leukemias, malignant lymphomas, and multiple myelomas (Archive of ophthalmology Jan 1978, VO (96, No.1) later the lens may become cataractous and its capsule may be ruptured and its fibres absorbed. Eventually by seeding and infiltration the neoplasm may invade all the ocular layers and cavities and perforate the globe. Endophthalmitis and panophthalmitis may occasionally supervene, extensively destroying the growth and quite obscuring its clinical presentation (13).

Diffuse infiltrating type:

This rare variant most commonly originates in the peripheral retina which is replaced, but only slightly thickened, by typical retinoblastomatous cells, mitotic activity, rosette formation and necrosis is not however marked. No macroscopic tumour mass is formed and retinal detachment is slight or absent but there is a constant discharge of malignant cells into the aqueous. In the course of time neoplastic cells replace the ciliary epithelium, infiltrate the ciliary body, uvodesceral meshwork and iris, and may invade the fundal retina and extend into the optic
central cavity 10-60 mm or more in diameter. The central cavity may contain a few neoplastic cells but never contains blood vessels. The lumen of the central cavity is demarcated by a limiting membrane through which the cells protrude short processes. This limiting membrane, which is the same type of the retinoblastomatous rosette, is made up of terminal bars and is analogous to the outer limiting membrane of the retina. The rosetted cells sometimes exhibit fine processes trailing out from their peripheral ends. Their resemblance to rod- and cone cells is impressive. Rosettes are rather constant in size and almost always circular or oval in outline but larger, elongated or horseshoe forms are occasionally seen. Rosettes are regarded as evidence of partial differentiation towards rod- and cone cells.

There is some evidence that the younger a retinoblastoma is, as judged by the age of the patient and the duration of the disease, the more rosettes it contains. Heavily rosetted growth are somewhat less lethal than those principally composed of undifferentiated cells.

PHOTORECEPTOR DIFFERENTIATION

More advanced differentiation of tumour cells to form photoreceptor elements occurs in a minority of retinoblastomas. Under low magnification, areas with photoreceptor differentiation are pale and eosinophilic compared with the densely basophilic areas of undifferentiated growth. This is because the differentiated cells have smaller, less hyperchromatic nuclei and more cytoplasm and separated by a relative abundance of intercellular matrix. These cells form eosinophilic cytologic processes 15-20 μm in length projecting through fenestrated membrane often in clusters like petals of a flower or a formal fleur-de-lys. Electron microscopy of these figures reveals that the cells of which they are composed show many similarities to and a few differences from the photoreceptors of normal retina. The absence of any evidence of Muller cell formation helps to confirm the belief that retinoblastomas are neuroblastic neoplasms. In areas showing photoreceptor differentiation, mitotic figures are rare, necrosis is absent and calcification deposition if present, is small in amount. There is evidence that cells showing photoreceptor differentiation are more radioreistant than undifferentiated retinoblastomas cells. This accords with the rule that the radio-sensitivity varies inversely with the degree of differentiation. Following radiotherapy, surviving tumour nodules composed of cells showing photoreceptors differentiation alone or mixed with glial tissue, have a grey translucent "fish flesh" appearance through the ophthalmoscope (ocular pathology G. H. Green) 4-3.
Beyond the retina to the other ocular tissue take place in the same two ways—by direct extension and by the seeding of cellular clusters through the vitreous and posterior and anterior chambers. Implantation growth are due to detached globules of neoplasms which may be deposited and grow on almost any site. The surface of the choroid, the retina itself, the iris, the ciliary body, the angle of the anterior chamber and the posterior surface of the cornea. Occasionally these are very extensive. The choroid may be invaded, the deposits at first lying upon the surface of this tissue without penetrating Bruch’s membrane. The iris may be covered with a layer of neoplastic cells or be sprinkled with nodules so as to simulate a tuberculous uveitis alternatively, as we have seen, a multitude of fragmented globules of the tumour may fill the anterior chamber making the aqeous turbid and be deposited as a hypopyon. Implantation growth have even been transferred on a graft from cornea of the donor eye of another host (Hata, 1939).

Direct extension usually first affect the dura, the tumour frequently extending along the vessels near the disc, frequently also new-formed vessels near the ora pass from the retina to the anterior area of the choroid and carry a direct extension in this way. Clinically such extension is very difficult or impossible to diagnose until it has reached a considerable size. The spread is first noted as a diffuse yellowish mass developing on the side along the border of the tumour or even completely encroaching into or on its surface the retinal lesion may seem to preserve its extension into the optic nerve which is invaded in one of two ways, either by direct spread from the retina or by extension from the choroid into the vitreous space. From the retina the neoplastic cells make their way through the lamina cribrosa first around the central vessels. It is rare, however, for this direct involvement of the nerve itself to extend for any great distance, for it follows the central vessels as they leave the nerve to reach the sub-arachnoid space. The alternative method of spread to the sheath of the optic nerve is from the choroid by direct extension across the border tissue without initially invading the nerve itself. Once the sub-arachnoid space has been reached spread rapidly follows to the chiasma and brain. When the tumour cells involve the chiasma the IIIrd ventricle is frequently involved and internal hydrocephalus may result, the pituitary gland closely related to the chiasma and are frequently
infiltrated by the growth while the subarachnoideal space of the opposite nerve may be invaded causing proptosis or papilloedema. It would seem, however, that the dura forms an barrier to this mode of spread for the bones of skull, although they may be eroded by pressure, are not invaded by the secondaries in the meninges. This type of spread accounts for approximately half the fatalities resulting from retinoblastoma. (8-9)

Direct Extension into the orbit:

Is not uncommon usually from large tumour which has destroyed the globe, the spread often takes place as discrete cells and not as gross tumour and these may travel through the sclera by infiltration or along the emissary vessels. Liberated from confines of the globe the extension grows rapidly, protrudes as a fungating mass between the swollen lids and tends to spread directly to the nasal cavity, to the opposite orbit or to the cranium through the cribriform plate so that respiration and deglutition become impossible, such a condition is not only a grave danger to life but presents considerable difficulties in management. Once the orbit has been invaded dissemination into the blood-stream and involvement of the neighbouring lymph nodes usually occur rapidly with a fatal termination. (13)

THE LYMPHATIC SPREAD

Along the orbital lymphatics after the manner of carcinoma and unlike the usual malignant melanoma, tends first to be in the vicinity of the eye, to the pre-auricular and cervical nodes and to the bones of the skull and face. Thence the lymphatic spread may be diffusing involving the mediastinal, axillary, abdominal, inguinal and other nodes, since the orbital invasion is by discrete cells not clinically visible, such extension is readily missed on excision of the eye, recurrences are therefore common in socket after the globe has been enucleated, the average time of recurrence being 5-1/2 months, but they are sometimes long delayed (9 years) after enexenteration of both orbits and treatment by radiotherapy and chemotherapy. The first sign of this catastrophe is a swelling of the lids or displacement of a prosthesis if one has been fitted, while the lids become gradually separated by a raw, leathery looking mass. (17)

METASTASES BY BLOOD-STREAM:

Are also common, the choroidal invasion being probably main route of identity, but the general picture for long resembles that of retinoblastoma at alster stage an extensive bullous detachment of the retina may develop. Histologically the youngest deposits are found in the outer layers of the choroid among the larger vessels where the cells from aggregations between the tissue-planes,
attacked by growth along perforating vessels, but the cornea is usually not involved until a later stage when invasion occurs most frequently through the trabeculae but sometimes through ruptures in descemet's membrane caused presumably by stretching. thereafter multiple ruptures howman's membrane are common through which columns of cells spread under the epithelium.

which these neoplastic changes are progressing a general degeneration occurs through out the ocular tissues. the retina atrophies to become a thin fibrous membrane in which some evidences of the nuclear layers remain, the whole of the neural structures disappearing and the subretinal space being filled with a coagulable transudate. the pigmented epithelium varies between proliferative and degenerative change. optic atrophy is evident at any early stage, the fibres degenerating as a result of the complete retinal optic atrophy, while the clinical appearance of atrophy is later, accentuated by the formation of deep glaucomatous cup which however, is invariably filled up in time by new growth the vitreous which however, may contain avascular metasstatic clumps of cells, may remain clear for a long time but eventually breaks up, sometimes with the formation of membranes, these if they stretch behind the lens, may cause difficulties in clinical diagnosis, the choroid also atrophies and subchoroid becomes obliterated, before the tissue itself is permeated with growth. a similar extent atrophy affects the ciliary body and also the iris which becomes attenuated, vascularized, and show an ectropion of its pigment layer. this atrophy of the iris showing lacunae, the lens also suffers, being pushed forwards and deformed, and sometimes becoming absorbed so that the only capsule remains, the sclera become stretched and thinned, a staphyloma occurring in the ciliary region, while in the cornea the increasing pressure causes multiple tears, and ulceration and eventual perforation with a proliferation of the growth through the wound may be expected in cases which have been allowed to progress. in exceptional instances the whole globe may become atrophic and shrink most usefully, perhaps after it has been perforated. (10-13)

extra-ocular extension : -

occurs along two routes : - (1) to the brain and (2) the orbit. endophytic type a simple detachment of the retina may by simulated, an appearance which, however, when occurring in young
children, should always be reviewed with the greatest caution. In this case transillumination may be of some value, a method not by any means to be overlooked in finding the type of tumour, but an area of relatively poor translucency may be demonstrated beneath the detached retina, more over retinoblastoma exhibits a bright diffuse glow during the arterial and venous phases of the intraocular injection of fluorescein. In both cases the ophthalmologic appearance of calcified areas can be taken as being diagnosis. In this connection radiography should supplement the clinical examination, for over 75% of cases calcium in the tumour can be demonstrated as a characteristic mottled deposit. As growth progresses difficulties in the clinical picture may arise from the presence of vitreous opacities or dense membrane stretching behind the lens, but in later stages the occurrence of pseudo-hypopyon of tumour cells, the early appearance of atrophy and the later development of nodules in the iris, and the eventual filling of the entire eye with neoplastic tissue is present apilatus which is only too obvious. In the earlier stage when the condition resembles an iridocyclitis, a panorectant of the anterior chamber may be undertaken in which case multinod cells may be found, but this lead to spread, it is interesting that the diagnosis may be confirmed by finding retinoblastoma cells in the c.s.f withdrawn by l.p. escape, but neoplastic cells may invade the central retinal vein while the exuberance of the growth in the orbit makes extension of the common source. Thence secondaries appear in quantity in the distal bones (especially the vertebrae, the ribs and sternum and the bones of the limbs, the viscera, especially the liver-spleen, pancreas, spleen, lung ovary and testes) the most common site are the bones and the liver, the ultimate cause of death in this is by no means always intraocular spread as generally stated, but is very frequently a widespread metastatic dissemination through the blood stream (Duke elder page 706) (10 - 13).

DIAGNOSIS:

The diagnosis of retinoblastoma is frequently difficult considering the vital importance of tissue involved, however, such cases should always must be examined under anesthesia after full dilatation of the pupil, particularly is care necessary in searching for involvement of the second eye, since small tumours are not uncommon for in the periphery, in the initial and the frequent follow-up examinations which are essential for several years. Indirect ophthalmoscopy and scleral indentation should be practiced. Two general features are of importance in distinguishing this neoplasm from several other condition, a retinoblastoma rarely occurs in microphthalmic or deformed eye, and ocular tension is normal or raised.

The appearance of small tumours is usually typical although it may be difficult in exophytic cases when it lies beneath the
retina, as it grows and reaches the stage at which, is generally first seen, in the common endophytic type the grey-white nodular vascularized mass in the vitreous is often unmistakable.

The eventual stage of extra-ocular extension when an ulcerating and bleeding fungoid mass protrudes behind the lids is simulated by nothing else in young children except perhaps orbital deposits of ophthic neuro blasts. The diagnosis is confirmed by excision and histological examination.

DIFFERENTIAL DIAGNOSIS 1-

This include a considerable number of conditions -

In the early stages the lesion in the fundus may be simulated by an inflammatory condition such as metastatic retinitis, a tubercu- loma or brucellosis, or a parasitic infestation such as toxoplasmosis toxocarasis or cysticercosis. A congenital deformity such as a coloboma or medullated nerve fibres may rise to anxiety, or a neoplastic lesion such as an astrocytoma, a dicytoma, a choroidal malignant melanoma, angiomatosis or tuberculous sclerosis. In the later stages when the posterior segment of the eye is so occupied organized tissue as to produce an amurotic cat's eye, the differential diagnosis is more difficult and frequently impossible it should be repeated that when doubt exists, such a blind eye should be excised. These conditions traditionally called pseudo glioma but now more happily leukocoria embrace the following lesions-

1- inflammation, usually due to an acute infective disease, tuberculosis, syphilis, or toxocara. There may be a history of a red, irritable eye and the presence of inflammatory signs, frequently with a lowered tension.

2- Intra-ocular haemorrhage, usually occurred at birth, which has become organized.

3- Retrolental fibroplasia, occurring bilaterally in a premature in- fant.

4- Persistence of the vascular tunic of the lens (persistent hyperplastic primary vitreous occurring in a full-term infant unilaterally in a slightly microophthalmic eye. The small lens and the mass is typically vascularized with old vessels.

5- Encaphalo-ophthalmic dysplasia, affecting full-term infant bilaterally, the eye is microphthalmic and there are associated cerebral symptoms.

6- Retinal septum (faciform folds)

7- Congenital detachment of the retina is very rare, so also retinoschisis.

8- Coats's disease, occurring unilaterally in males.

9- Infusionstatis of the retina, usually occurring bilaterally in either sex.

10- Congenital cataract from any cause including infection by rubella virus.

11- Traumatic retinal detachment.
12- Medulloepithelioma.
13- Norrie disease, this rare recessive X-linked hyaloideoretinal dysplasia results in congenital blindness in both eyes.
14- Telarang 13-15 which cause ocular defects ranging from congenital cataract to anophthalmia.
15- Endophthalmitis.


TREATMENT:

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In view of exceptional rarity of the favourable event of spontaneous regression, the only legitimate treatment to try for a retinoblastoma is its destruction as early as possible. For this purpose two standard methods have been established, enucleation of the eye, exenteration of the orbit, and radiation, destruction by photocoagulation or diathermy is less reliable unless the neoplasm is small but both are useful auxiliary techniques, while treatment by cytotoxic agent is indicated in advanced cases and as palliative when local or metastatic spread has occurred. (5-19).

ENCELEATION:

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Enucleation of the globe is the most effective opportunity and safe for treatment of retinoblastoma. In the operation the importance of excising as long as a portion of the optic nerve as possible cannot be overstressed, as and secured by pulling on two traction sutures passed through the insertions of the two horizontal rectus muscles to put the optic nerve under tension and then passing the blades scissors backwards along the nasal wall of the orbit towards the optic foramen but avoiding cutting the funnel of muscles. We have already seen that prolonged extension up the nerve itself rarely occurs so that it is probably safe if 10 mm. behind the globe are removed. If extension has taken place up the sheath of the nerve, spread is usually rapid and cannot be surgically removed. Immediately after the operation the cut end of the nerve should be sectioned transversely, if any extension to this point has occurred, radiotherapy and chemotherapy are required. Whether an orbital implant should be inserted is
questionable, it undoubtedly aids the normal development of the
orbit of the child but obscures early orbital recurrences, a
plastic implant, however, has little or no effect on subsequent
radiation.

Since the extreme importance of extension up the nerve in
determining the prognosis has realised, the results of operative
treatment have been improved, a point well brought out in
literature thus Hirschberg (1869) obtained a survival rate of 6.5%
and Adam (1916) of 57% a figure retained to present day (53%
Reese, 1931-63). (10)

In view of the method of spread up the nerve it would seem that
an intracranial-orbital operation is unnecessary—either an
extension of the nerve from the chiasma subsequent to the
enucleation (Dott and Neighan 1939, Rand 1934) or the same
intracranial procedure carried out before enucleation (Kay and
McLean 1943). If orbital extension has occurred, its extension has
been advocated, a somewhat drastic procedure, however, which
might well be replaced by radiational treatment unless the
invasion is gross. (10).

RADIATION-

Radiational treatment, has been practised since Hilgstoer (1933)
demonstrated that retinoblastomas were radio-sensitive. Indeed,
more so than the radio-resistant retina itself, but X-rays
have been used more extensively since Verhoeff (1921) showed that
with suitable doses of radiation the eye and reasonable vision
could be retained. That radiation can be effective has been proved
by the histological demonstration of widespread necrosis in the
tumour after its application (Stallard, 1933, Fewell and Fry, 1935)
and the resultant clinical appearance is that a quiet fibrosed
scar involving both the retina and choroid.

At first with general radiation of the globe the results were
unsatisfactory, on one hand, the tumour remaining viable, and on
the other, gross desiccation being done to the eye owing to
radiosensitivity of the structures of the anterior segment,
particularly the lens and the ciliary body with a modern posterior
segment technique however, where in the anterior segment of the
globe is safeguarded and with controlled dosage, the results of
radiation have been much more satisfactory, a gratifying advance
largely due to the work of Reese and his collaborators, particularly
when combined with the use of cytotoxic drugs in advanced cases.

Reese finds recommends was a dose of radiation on the tumour
no more than 3,500 r in multiple daily treatments over 3 weeks
using a supervoltage apparatus, temporal and nasal. He advised
22.5 mev cobalt betastron with which the dose on the surface is
cosiderably less than that on the tumour and the beam has a sharp
edges with little side scatter, while the child, necessarily
sedated, is immobilized in a flexicast jacket this technique is
undoubtedly ideal, but the equipment of a normally furnished
combination with x-radiation, and has been most fully exploited in this way by Reese and his colleagues (1953-63) who used triethylene melamine (TEM) while others have used the less toxic TEY-cyclophosphamide (INDOVA) (Stellard 1962 (10)). These drugs of course, are all toxic and therapeutic effects result unless a considerable haemopoietic depression also develops (leucopenia thrombocytopenia) which method or which combination of techniques should be chosen in any particular case depends largely on the size and stage of development of the tumour, whether it is unilateral or bilateral, or whether orbital, intracranial, or metastatic spread has occurred. To assess this before any treatment is embarked upon, a careful preliminary assessment of the case should be made. This involves a minute examination of both retina in their entirety including the extreme periphery, particularly in apparently unilateral cases, under an anaesthetic and with full mydriasis, a radiographic examination of the optic canals, orbits and skull, a neurological examination of the central nervous system, an examination of the cerebro-spinal fluid for neoplastic cells and of the bone marrow for evidence of metastases. In the assessment of the value of the various methods of treatment available it is to be remembered that x-rays and chemotherapy are general agents attacking any neoplastic area through out the retina, while the action of radio-active applicators, photo coagulation and diathermy is limited to one local site an important point in view of the multicentricity of many retinoplastic cases (10).

If the tumour is unilateral and small, x-radiation is not particularly appropriate since the nasal portal cannot be used because of the fellow eye, a radio-active applicator (for tumour less than 15mm in diameter) is probably more effective and may be considered as alternative to x-radiation. If any residual areas are left after treatment they should be destroyed by photo coagulation, unilateral cases, however are usually for advanced or multiple when are first seen, and if more than 1/3 of the retina is involved in one or more growth or if there is fragmentation into the vitreous the eye should be enucleated. If histological examination shows spread up the optic nerve super voltage radiation (up to 4,500r in 4 weeks) should be given. In the assessment of this type of case it is to be remembered that a number of so-called unilateral tumour become bilateral within two years. If the tumour becomes bilateral and for advanced in one eye the latter should be excised and the diagnosis histologically confirmed. Every effort should be made to salvage some vision in the other eye as the preferable course to the dreadful alternative of the excision of both eyes of a child. Although many who have been blind from infancy have lived long, useful and happy lives, bilateral enucleation is a horrible procedure, but less for the surgeon than for the parents, but less distressing than the alternative inevitable end, the decision, with all its bearings and its uncertainties, its best shared between both parties. If
both eyes are blind this course is obvious. If the neoplasm in the second eye is small, bipoortal or catheterization radiation with the technique of REHUE combined with chemotherapy gives best results particularly if more than one lesion is present (10). If the lesion is single or not more than one or two are present and in a suitable position, radio-active cobalt applicators with chemotherapy are as effective but do not carry the same hope of destroying other occult but potential sites of the growth which may not be clinically visible, these are not unusual in bilateral cases. Any suspected sites of retinal recurrence can be treated with photocoagulation. If spread has occurred to the choroid the intense radiation at the base of the tumour makes the technique of a radioapplicator suitable. If resistance is shown to radiation it may be repeated, although further courses of general radiation usually lead to complications necessitating removal of the eye, an applicator can still be safely used. Orbital recurrences are usually treated by exenteration, if they are gross and subsequent radiation with chemotherapy and metastatic deposits can only be unsatisfactory palliated by radiation associated with the use of cytotoxic drugs. Follow-up examinations are essential in every case on each occasion conducted under general anaesthesia, at least at 4 months intervals for 2-3 years and there after 6 months for the next 2 years and probably yearly for the next 3 years probably that the patient is safe after interval of 3 years although recurrences after longer periods have been recorded wherein the tumour has apparently remained in a state of suspended viability. The earliest sign of recurrence in a treated neoplasm is the appearance of pink flush due to formation of new capillaries, any subsequent increase in size should be checked by repeated fundus photography. System of ophthalmology Duke - Elder.

PROGNOSIS

Treatment by irradiation is an alternative to enucleation of the eye. The probable response to irradiation can be rather accurately judged by classifying the tumours into groups according to their size, number and location in the eye.

1. If enucleation is done, as much optic nerve as possible should be removed with the globe and examined histologically. If the nerve is free of growth and there is no evidence of orbital extension, risk of recurrence is not great and prognosis will largely depend on the probability of a second neoplasm developing in the affected eye. This probability is greatly increased when there is inherent liability to the disease. If the second neoplasm does appear, the prognosis still remains quite favourable provided the growth is promptly and totally eradicated. Estimates of cure by enucleation alone, in cases without evidence of extraocular extension, vary from 50 - 90% of cases. Early apprehension and prompt enucleation naturally increase the percentage.
2- If the optic nerve is infiltrated, the growth has extended through the lamina cribrosa, the outlook is much worse. A fatal outcome is to be expected in approximately 50% of such cases. If the growth has extended to the point of axis of the central retinal vessels from the nerve, the mortality rate rises approximately 65%.

3- If neoplastic infiltration extends to the cut end of the optic nerve the line of excision has passed through malignant tissue. Recurrence is then almost certain and prognosis is grave. Recurrence, which usually occurs within 6 months of enucleation, is most commonly in the orbit but occasionally within the cranium or even at some distant metastatic site.

4- Spontaneous regression of retinoblastoma is very rare and is probably always due to massive necrosis followed by calcification and ossification. The possibility that in some instances regression is the result of a cell mediated immune reaction deserve consideration. In almost all authentic cases regression occurred in one neoplasm of a bilateral pair. (6-10-13).
MATERIALS and METHODS
Material and Methods:

Thirty six consecutive, unsellected retinoblastoma patients, coming from different regions of the Sudan, were studied at Khartoum eye hospital between March 1985 to March 1986.

Age, sex, family history, social history, residence, tribe, parental consanguinity, pregnancy history, time of onset and developmental history were recorded.

Also the involved eye, mode of presentation, and the clinical course were recorded.

Full examinations were done including the local examinations of the globe, the orbits. General examinations of the patient including the all systems and conscientation were done particularly in the liver and the lymph nodes.

Examinations under anaesthesia after full dilation of the pupils was done searching for involvement of the second eye. Indirect ophthalmoscopy was done for these patients.

Radiological examinations were done. Also photographs were taken for these patients including the different views.

Management of the patients including the following:

1. Enucleation of involved eye: was done after taking the consent of the parents. Done under general anaesthesia. Using a clone to pull the involved eye and take as much as possible of the optic nerve.

2. The excisional biopsy was sent for histopathology and a report was obtained.

3. The affected child was referred to the radiotherapy department.

Follow up:

This was found difficult because the patients came from far areas; it was not possible to assess prognoasia in these patients.
RESULTS

---

Age:

The age of the patients at the time of diagnosis was between 6 months and 5 years. (Table 1).

6 patients from age 6 months to one year,
10 patients from one year to two years,
9 patients from two years to three years,
5 patients from three years to four years,
6 patients from four years to five years.

Sex:

---

Table (2)

From 36 patients, 17 patients were males and these about 47.2%.
Females were 19 patients and these about 52.8%.

Source:

---

Table (3)

The thirty six patients were coming from different regions of the Sudan.

11 patients from Darfur region, this about 30.6%
8 patients from Northern region this about 22.2%
7 patients from the Central region this is about 19.4%
5 patients from the Northern region this about 13.9%
2 patients from Khartoum province and this about 5.5%
2 patients from the Southern region and this about 5.5%
1 patient from the Eastern region and this about 2.2%
### Sex

**Table (2)**

<table>
<thead>
<tr>
<th>Sex</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>47.2%</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>52.8%</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Figure (2)

![Figure](image)

### Source (region)

**Table (3)**

<table>
<thead>
<tr>
<th>Region</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darfur</td>
<td>11</td>
<td>30.5%</td>
</tr>
<tr>
<td>Kordofan</td>
<td>8</td>
<td>22.2%</td>
</tr>
<tr>
<td>Central</td>
<td>7</td>
<td>19.4%</td>
</tr>
<tr>
<td>North</td>
<td>5</td>
<td>13.7%</td>
</tr>
<tr>
<td>Khartoum</td>
<td>2</td>
<td>5.5%</td>
</tr>
<tr>
<td>East</td>
<td>1</td>
<td>2.2%</td>
</tr>
<tr>
<td>South</td>
<td>2</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>100%</td>
</tr>
</tbody>
</table>
RESULTS

Age

(table 1) Age at the time of diagnosis

<table>
<thead>
<tr>
<th>Age</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) 6 month - 1 year</td>
<td>6</td>
<td>18.7%</td>
</tr>
<tr>
<td>(B) 2 years</td>
<td>10</td>
<td>27.7%</td>
</tr>
<tr>
<td>(C) 3 years</td>
<td>9</td>
<td>25%</td>
</tr>
<tr>
<td>(D) 4 years</td>
<td>5</td>
<td>14.1%</td>
</tr>
<tr>
<td>(E) 5 years</td>
<td>6</td>
<td>16.6%</td>
</tr>
<tr>
<td>(F) 6 years</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>100%</td>
</tr>
</tbody>
</table>

Figure (1)

10
8
6
4
2

6/12-1 - 2 yrs - 3y - 4y - 5yrs
Table (4)
The tribe of the patients as follows:

<table>
<thead>
<tr>
<th>Tribe</th>
<th>Number</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaallen</td>
<td>5</td>
<td>Poor</td>
</tr>
<tr>
<td>Nooba</td>
<td>3</td>
<td>Krd</td>
</tr>
<tr>
<td>Zagawa</td>
<td>2</td>
<td>Cent</td>
</tr>
<tr>
<td>Canqua</td>
<td>2</td>
<td>North Krt</td>
</tr>
<tr>
<td>Bezega</td>
<td>2</td>
<td>South Krt</td>
</tr>
<tr>
<td>Falatta</td>
<td>2</td>
<td>Krd</td>
</tr>
<tr>
<td>Nagarba</td>
<td>2</td>
<td>Cent</td>
</tr>
<tr>
<td>Kenana</td>
<td>2</td>
<td>North Krt</td>
</tr>
<tr>
<td>Kwaha</td>
<td>2</td>
<td>South Krt</td>
</tr>
<tr>
<td>Borno</td>
<td>1</td>
<td>Poor</td>
</tr>
<tr>
<td>Messeria</td>
<td>1</td>
<td>Krd</td>
</tr>
<tr>
<td>Shabla</td>
<td>1</td>
<td>Cent</td>
</tr>
<tr>
<td>Mohanodis</td>
<td>1</td>
<td>North Krt</td>
</tr>
<tr>
<td>Madr</td>
<td>1</td>
<td>South Krt</td>
</tr>
<tr>
<td>Beny Amir</td>
<td>1</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Parental Consanguinity:

31 patients had a positive parental consanguinity and thus about 86.12%.
5 patients had a negative parental consanguinity and this about 13.9%.

Table (6)

Represent that 26 patients had first degree parental consanguinity and this about 72.2% from the total. 2 patients had second degree parental consanguinity and this about 5.6%. 3 patients had third degree parental consanguinity and this about 8.4%.

<table>
<thead>
<tr>
<th>Tribe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>5</td>
</tr>
<tr>
<td>Gaalen</td>
<td>5</td>
</tr>
<tr>
<td>Nooba</td>
<td>5</td>
</tr>
<tr>
<td>Zagawa</td>
<td>3</td>
</tr>
<tr>
<td>Gammola</td>
<td>2</td>
</tr>
<tr>
<td>Bezegat</td>
<td>2</td>
</tr>
<tr>
<td>Fatata</td>
<td>2</td>
</tr>
<tr>
<td>Mogarba</td>
<td>2</td>
</tr>
<tr>
<td>Kenana</td>
<td>2</td>
</tr>
<tr>
<td>Kwalla</td>
<td>2</td>
</tr>
<tr>
<td>Borno</td>
<td>1</td>
</tr>
<tr>
<td>Messeria</td>
<td>1</td>
</tr>
<tr>
<td>Shanabia</td>
<td>1</td>
</tr>
<tr>
<td>Mohoedia</td>
<td>1</td>
</tr>
<tr>
<td>Nadi</td>
<td>1</td>
</tr>
<tr>
<td>Beny Amir</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

Parental Consanguinity

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>tve p.c</td>
<td>31</td>
<td>86.1%</td>
</tr>
<tr>
<td>+ve p.c</td>
<td>5</td>
<td>13.9%</td>
</tr>
</tbody>
</table>
Time of onset:

the age at the time of first symptoms (table 7).

1 patient since birth and this about 2.8%
5 patients from 6 months to one year and this about 22.2%
7 patients from one year to two years and this about 19.5%
10 patients from two years to three years and this about 27.8%
7 patients from three years to four years and this about 19.5%
3 patients from four years to five years and this about 8.2%

Eye Involved

Table (8)

26 patients represented by unilaterial retinoblastoma and this about 72.2%
10 patients represented by bilaterial retinoblastoma and this about 27.8%

Table (9)

In unilater retinoblastoma:

10 patients represented by retinoblastoma of the right eye and this is about 27.8%
16 patients represented by retinoblastoma of the left eye and this is about 44.4%

Presenting symptoms and signs

Table (10)

11 patients presented by leukocoria and this is about 30.5%
17 patients presented by ocular mass and this is about 47.4%
5 patients presented by ocular mass in one eye and leukocoria in the other and this is about 13.9%
1 patient presented by squint and this is about 2.7%

Figure (4) Parental consanguinity
Time of Onset: Age at time of first symptoms

<table>
<thead>
<tr>
<th>Time</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>since birth</td>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>- 6 months</td>
<td>8</td>
<td>22.5%</td>
</tr>
<tr>
<td>- 1 year</td>
<td>7</td>
<td>19.3%</td>
</tr>
<tr>
<td>- 2 years</td>
<td>10</td>
<td>27.6%</td>
</tr>
<tr>
<td>- 3 years</td>
<td>7</td>
<td>19.5%</td>
</tr>
<tr>
<td>- 4 years</td>
<td>3</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Figure (5)

Eye affected

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One eye</td>
<td>26</td>
<td>72.2%</td>
</tr>
<tr>
<td>Both eyes</td>
<td>10</td>
<td>27.8%</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>100%</td>
</tr>
</tbody>
</table>

Figure (6)
### Involving eye

<table>
<thead>
<tr>
<th>Eye</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>10</td>
<td>27.8%</td>
</tr>
<tr>
<td>Left</td>
<td>16</td>
<td>44.9%</td>
</tr>
</tbody>
</table>

### Presenting symptoms and signs

**Table (10)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocoria</td>
<td>11</td>
<td>30.5%</td>
</tr>
<tr>
<td>Ocular mass</td>
<td>17</td>
<td>47.4%</td>
</tr>
<tr>
<td>Bl. Leukocoria</td>
<td>2</td>
<td>5.5%</td>
</tr>
<tr>
<td>Ocular mass + Leukocoria</td>
<td>5</td>
<td>13.9%</td>
</tr>
<tr>
<td>Squint</td>
<td>6</td>
<td>16.7%</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Figure (7)**

```
  20
  16
  12
   8
   4
Leuko  C.mass  Bl.Leak  C.mass + Leuk  Squint
```
Sex

From our study of the thirty-six patients, 17 were males and this was about 47.2%, and 19 were females and this was about 52.8%. Therefore, the neoplasm showed no preference for any sex. Also, the international results.

Regions (source)

Referring to table (3) we observed that, 11 patients were from Darfur region (30.5%), and 8 patients were from Kordofan region (22.2%). Therefore, from our thirty-six (36) patients, 19 patients from the Western region (52.7%). Also, putting in mind the patients came from far areas to the hospital from these two regions, this indicated the high prevalence of retinoblastoma in the West of Sudan compared with the other regions. We thought that genetic backgrounds must play a role here rather than geographical distribution.

Most of the patients from Darfur and Kordofan region.
TRIBE

On thirtysix patients came from (16) tribes. We observed increased presentage in certain tribes. Poor, Nooba and Hamil tribes representedby 5 patients for each one. So about 41.2% of the patients from these 3 tribes. If we added Zgawa tribe (4 patients), this means 50% of the patients from 4 tribes. Also a valuable observation is the decrease of incidence in Eastern tribes.

Social history:

Almost all the patients from families of low socio economic status. Most of their fathers were farmers or workers of low income.

Family history:

It was very difficult to take a proper history from most of the patients relatives. For this reason it was so difficult to know any positive family history of retinoblastoma in the previous generations of these affected patients. It was interesting report two cases, two sisters presented to us with bilateral retinoblastoma.

The first case her name was Ekram Osman Khalid, her age was three and half years presented with right proptosis and left leukocoria. The second one her name was Elham Osman Khalid, her age was one and half years, presented with bilateral leukocoria.

Residence: El Mannagil from the central region.

Tribe: Mogarba tribe.

Clinical diagnosis of retinoblastoma was reached form the two sisters and E. U. A for the two patients was done. The diagnosis was confirmed by histopathology after exculation done for one eye of each patient, and they were send to the radiotherapy department to continue their management.

The two sisters. Both had bilateral retinoblastoma.
Prevalent Consanguinity: Table (5) and Table (60)

High percentage of the family relation of the affected children. It was found that about 86.15 of the cases had parental consanguinity. Most of this relation of the first degree (72.12). Therefore this may give an evidence that genetic factors play an important role of developing retinoblastoma.

Even most of the patients who had negative parental consanguinity, their parents are from the same tribe.

Pregnancy and labour history:

Almost all the mothers gave a normal history during pregnancy and labour of their children.

So there was no history of exposure to potential teratogens, no history of rubella, radiation or drugs. Also the mothers gave a normal labour history, i.e. all of them were normal delivery and full term and no history of taking drugs or oxygen or had respiratory distress syndrome, because these will cause retrolental fibroplasia.

Also the parents gave a normal developmental history for their children.

Also there were no associated features like mental retardation or Down syndrome.

Time of onset of retinoblastoma:

Also it is very difficult to know the exact time of onset of retinoblastoma in Sudanese patients. And always there was a difference between the saying of the parents. Because also the medical care in these areas is very low. For these reasons observations to know the early eye changes of retinoblastoma in our patients was delayed. Referring to Table (9) only one case observed after birth. The peak between 1-2 years.

Comparing the time of diagnosis (Table 1) with that when the first changes observed by the parents, there was delay for bringing children to the hospital.

Hye affected:

Referring to Table (8) 27.8% of the patients in our series presented with tumour in both eyes. This percentage is very suitable as compared with other series reported from 20 to 40 percent bilateral tumours. In some institutions that concentrate on patients with bilateral tumours up to 77.7% has been reported. Since we have been unable to follow our patients postoperatively, we do not know if any one of them developed retinoblastoma in the second eye, therefore it is possible that we may have missed some patients with bilateral tumours.
Conclusions

This thesis was done in Khartoum Eye Hospital between March 1985 to March 1986 for the clinical study of retinoblastoma. 36 patients of retinoblastoma were presented during this time. The objectives of this study mainly to investigate these cases according to their age and sex also to know the regional distribution and to know also their tribes. Another important objective is to see the effect of heredity and teratogenes in development of retinoblastoma this was done by taking full history about the parental consanguinity, any family history of proptosis, bilateral presentation of retinoblastoma and other related features to study the mode of presentation and the clinical course of the disease also to reveal the incidence of ocular mass presentation among these patients. After enucleation and obtaining of the histopathology report, the patients were referred to radiotherapy department. We faced another problem, the lack of the follow up. This because the relatives were poor and the problem of the transport. Analysis of this study was done, and we reached the following results:

The age at the time of diagnosis for the thirty six patients between 6 months and 9 years. And when a comparison between the age at the time of diagnosis, with the age at the time of onset, there was a delay and this mainly due to the delay of the observation by the relatives and mainly to the transport problems because the hospitals are far away from their residence. There is no sex discrimination in this study because we had 19 females and 17 patients males. From the study we had 19 patients (about 52-7) came from Western of Sudan, and this is a high percentage. We thought that this way be due to genetic basis rather than climate changes. An evident supported by presence of retinoblastoma patients of the western races living in other regions. There were three tribes had the highest percentage of retinoblastoma these were Nuba, Fur and Gaaliyem tribes, presented by 5 patients for each one this may support the rule of genetics in development of retinoblastoma. Almost all the patients from families of low socio-economic status. We found it was very difficult to take a proper family history. But among our series
we had two families both of them, presented with bilateral retinoblastoma.

A high percentage of parental consanguinity (about 86.1%) most of them (about 72.2%) of first degree relationship, this also goes with the genetic support of development of retinoblastoma. Regarding the pregnancy history and labour history and developmental history, no significant results were obtained. We found about 77.8% of presentation were bilateral, this percentage is very suitable as compared with other series reported from 20 to 40% bilateral tumours. Ocular mass presentation was found in about 47.4%, this high incidence to many factors e.g., the relatives refused to do the enucleation, so they changed from hospital to another hospital, and from one doctor to another.

The second presentation was leukocoria 39.5% and their relatives usually refused the operation, so the patient presented with advanced ocular mass. Radiological examinations were done for many patients but no calcification was detected. Management includes the enucleation and application of radiotherapy. Follow up was difficult so we found it was very difficult to assess the prognosis in these patients.
RECOMMENDATIONS
Recommendations

Health education is very important in early management of retinoblastoma, due to the fact that retinoblastoma has a good prognosis if detected early. So health education may help very much in decreasing the morbidity and mortality rates this by:

1. Early report to the hospital after observation any abnormal change in the globe.

2. To obey the advice of the doctors for enucleation.

3. Proper visits to hospital for follow up.
REFERENCES

(1) Albert Hornblow, Tumours of the ocular adnexa and the orbit. Chapter 25 page 273.


(7a) Sogky Armold's Modern Ophthalmology vol.1, page 186.
(19) Trevor Roger PD. The Eye and its disorders, the retina page 436.
**Pretorma For Clinical Study**

**OF RETINOBlastoma In K.E.H.**

---

**Date:**

**Name:**

**Age:**

**Sex:**

**Residence:**

**Tribe:**

**Social Hist.:**

**F. Hist.:**

---

**Partial Consanguinity:** 0123

**Pregnancy Hist.:** (Exposure to potential Teratogens)

- Radiation
- Drugs
- Others

---

**Labour Hist:**

- H.V.
- O.G.

**Condition at Delivery:**

- Full Term
- Premature

**Therapy After Delivery:**

- Drugs
- Oxygen
- Others

---

**Developmental Hist.**

---

**Time of onset:**

---

**Symptoms and Signs:**

- Mode of Presentation:
  1. Leukocoria
  2. M.V.
  3. Stigmaria
  4. Squint
  5. Inflammatory Signs
  6. Others

---

**T.A.:**

- R.P.
- P.R.
- Latissimus

---

**Pain:**

- 0123
- 0124
- 0125
- 0126

**Lids:**

- Eyelids
- Inflammation
- 0127
- 0128
- Hyperemia
- 0129
- 0130

---

**Ant. Chamber:**

- 0131
- 0132
- 0133
- 0134

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**R.E.:**

- 0135
- 0136
- 0137

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**Lenses:**

- Cataract
- Other Eye

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**Fusions:**

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**Other:**

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**Lymph Nodes:**

- Periocular 0138
- Cervical 0139
- Submandibular 0140

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**Liver:**

- 0141

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**Skull X-Ray:**

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**Chest X-Ray:**

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**Eye X-Ray:**

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Associated Features:
- Mental Retardation
- Down Syndrome
- Others

Histopathology
Management
Remarks:
العربية الصادرة في مكة العربية من أكثر الأوراق الصادرة التي تسبب الأثار الحالية.

لا تزال سهرة كبيرة من أهل العيد يكتبون شواهد تضامنهم في مكة العربية.

وقد نصب بها هذا الحاضر في سنين العهد، وأنا أتمنى ان يزحل به وحالة الإثارة.

تعداد عين السعرض عند حدوت العيد وتتسبب.

تعداد الجبن بالنسبي للمسار.

دراست أجيك من الإحكام والأثر في حدوت عدد العيد، ولكن عند مطابقة معرفة وجرد حالات مهينة للأخلاق وأثر دراج النادر.

وصفت طريقة تشغيل هذا العيد بالنسبة لحالات السراخ المختلفة وتسمية بين البالغين.

دراست طريقة العيد التي بثت بها وحالة الإثارة وما تبعه ضعف الساحة في الحضور.

الاستدامة وحالة العيد، وحالة الإثارة.

فلا تفوت فرصة معزول عن هذا الحاضر، نضحك تأثير العيد، وثورة الإثارة والمحفظ والنسبي وحالة القهر ولا يوجد وفاة وحالة قهر للأخلاق.

وقد نصب بها هذا أجراء شواهد تضامنهم في مكة العربية ونظام الإثارة.

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ودعنا نتمنى ان يتقلص هذا الحاضر وحالة الإثارة.
الترجمة بين الأقماط والتعاون:

من ناحية البناء، يتم ارتداد عواصم الإمارات بهذا المرصد في الأيام دادليد
وكرشتن حوالى 245٪ من الحالات. وتعزز هذه الارتفاعات وتراكم بالأكثر من أنها عرقل
بيئة أو مناح وق tweالعلاج اللاتيد جيلاما، بينما مكان الأقماط بهما في مواقع أخرى في
المرصد. وتعزز ارتفاع نسبة الإصابات بين ثلاثة فئات في: (1) الأول
(2) الفئات
(3) المشهور
(4) المجال

العلاج الاجتماعي:

نظام المساهمين تتوزع من أمام ذات ماثي مشيداً عانياً واجتماعياً.
أثر رياض الإبارب:

حدث هذا في عدود الحالات في أسرة تعرضت لهما بين الأموال والأوراق من الدورة
الأولى بنسبة 67٪ وكذلك من الدورة الثانية بنسبة 11٪، وهذا ما يزيد أثر الإدراج
الأوراقية في الأسئلة بهذا العرس الخيري.
البنك المصرف:

كان حوالي 22٪ من الحالات لم تلق على المرشد في البنوك البيضاء والبنك وذا ينطلق
إلى الإدراجات الثانية الأخرى وهي ما بين 60 - 40٪.
طريقة توجيه المرضى:

من الناحية الأخرى، يمكن أن يكون أن أuegos (5007) تأتي
إلى المستشفيات لزيارتها. وعندما يزور في أيام العيد أو أي يوم، وهذا في ظلية للنمية الآلية:
(1) تأتي ملاحظة توفير معلومات العرض بواسطة الإبارب.
(2) أن.Gr. في إحدى الحداثات المستشفي.
(3) مخرج الإرسالات، وبناء مستشفي.
(5) عدم الانتهاء بسرعة الانتهاء وذلك بإزالة القرن المائي ليلةًا للقارب. والدواء البيITALI.}

الانتهاء بسرعة الانتهاء هو في نهاية الامساك، ما يقل ضيقه في حالة المريض.

ومع ذلك، هناك أنواع أخرى من الامساك التي تختلف عن ما ذكرت في الامساك بسرعة الانتهاء، ولا تتأثر بأي مدة العلاج. وتأتي هذه الامساك بسرعة الانتهاء من المراقبين وذلك بإزالة المريض نورًا للامساك، عند فترات أي من حالات المريض. وكذلك إزالة الامساك بسرعة الانتهاء عند أثرها الإيجابي وتحذير المريض للامساك.