Orbital tumours in African children

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The differential diagnosis of proptosis in African children poses a bewildering number of possibilities (Davies, 1968). Many of these cases prove to be due to inflammation of neighbouring sinuses or to invasion of the orbit by parasites or fungi. Orbital tumours causing proptosis occur frequently, and a series of sixty cases of proptosis in childhood caused by neoplasms in the orbit is reviewed in this paper.

Materials and methods

The Department of Pathology, Makerere University, Kampala, has for many years provided the only histopathological service available in Uganda, a country of nearly 10 million people. During the period 1964 to 1968 biopsies from approximately 7,000 malignant tumours were studied histologically. This collection is at present under review and during this work it became apparent that a significant collection of orbital tumours had accumulated. Conditions such as pseudotumour, myelocoele, and ossifying fibroma, although not strictly speaking neoplasms, are included in this review in those cases in which a biopsy was required to confirm the diagnosis. Sixty cases of proptosis in patients under the age of 16 years were reviewed. Sections from all cases were stained with haematoxylin and eosin. Other stains used as necessary included PAS, Glees Marsland for neural elements, reticulin stains, PTAH, Fontana, and the naphthol AS-D chloroacetate esterase reaction in suspected cases of chloroma.

Results

The diagnoses made in the sixty cases are shown in the Table. There were forty males and twenty females, the male excess being least marked in cases of Burkitt's tumour. Children with Burkitt's tumour were aged between 3 and 15 years (mean 7.3): sixteen male and twelve female.

The youngest patient with chloroma associated with acute myeloblastic leukaemia was a child aged 1 year, but otherwise the ages ranged from 5 to 12 years. The peripheral blood was normal in two cases though the marrow always showed leukaemic changes.

Three of the six patients with orbital myelocoele presented before the age of 6 months except for one child first seen at the age of 3 years. Five out of these six patients were males.

Six cases of fibrous dysplasia causing proptosis were seen and again five of the six patients were males; the average age at presentation was 10 years.

Only two out of seventy patients with nasopharyngeal carcinoma (lymphoepithelioma) presented because of proptosis; one was aged 12 and the other 15 years. The commonest presenting sign was that of lymph node enlargement with or without symptoms of nasal obstruction.

Orbital rhabdomyosarcoma is seen fairly frequently in Uganda, but it so happened that, although six cases were recorded in 1963, only one was seen in the period of this survey (1964-1968).

Table *Diagnoses in sixty cases of proptosis in African children thought to be due to tumour at the time of operation.*

Burkitt's tumour	28
Chloroma	8
Myelocoele	6
Fibrous dysplasia	6
Pseudotumour	3
Nasopharyngeal carcinoma	2
Rhabdomyosarcoma	1 case each
Fibrosarcoma	
Haemangioma	
Retinal anlage tumour	
Aesthesioneuroblastoma	
Neuroblastoma	
Malignant neurilemmoma	

Other tumours seen included one case each of malignant neurilemmoma, fibrosarcoma, haemangioma, retinal anlage tumour, and aesthesioneuroblastoma. Metastatic neuroblastoma was seen only once in a 3-year-old child from Busoga District.

Tribal distribution varied with the type of tumour. Both nasopharyngeal carcinoma and anterior myelocoele appear to be much more common in Nilotic tribes. Burkitt's lymphoma was seen most commonly in children from the north and north-west of the country and in none from the south-west, thus confirming the well-known geographical variation reported by Burkitt and Wright (1966). Most of the patients with chloroma lived around the city of Kampala, but this is probably due to a selection bias, since the only specialist haematologists and ophthalmologists in the country are to be found there.

Two tumours in this series appear to be unique for the orbit. Retinal anlage tumour, in spite of its name, occurs most frequently in the maxilla, and no case was found in the available literature in which orbital involvement was recorded. Aesthesioneuroblastoma usually presents as a nasal tumour, but in this case symptoms relating to the nose were minimal in a child aged 3 years presenting with proptosis. Details of these two cases are given below.

CASE 1. MELANOTIC NEUROECTODERMAL TUMOUR OF INFANCY (RETINAL ANLAGE TUMOUR)

A 5-month-old male infant of the Bakiga tribe presented with a swelling of the lateral side of the orbit, displacing the eye upwards and medially. On palpation this was woody and hard, and was shown by x ray examination to contain flecks of calcium.

At operation a charcoal-grey mass was found infiltrating the zygomatic bone. This was scraped out and no connection was found between the tumour and either the globe or the maxilla. The child did well after the operation and was noted to be in good health 3 months later, but thereafter was lost to follow-up.

Histologically the tumour consisted of epithelial cells of two distinct types arranged in islands in a background of fairly plump spindle cells. Since the mass had been removed piecemeal it was impossible to assess whether any capsule had formed but clinically there was none. Stain for neural fibres (Glees Marsland) proved negative. The smaller and darker epithelial cells were sometimes arranged in alveoli. The larger cells appeared in association with pigment which bleached with hydrogen peroxide and stained positively with Fontana. This pigment was also seen to be scattered

throughout the tumour extracellularly. The two types of cell were sometimes seen in close approximation but in no area could any convincing signs of organoid arrangement be found. However, in some areas, the paler cells became elongated and bore some resemblance to the rods of the retina (Fig. 1).

FIG. 1 *Retinal anlage tumour, showing the larger pigmented cells closely approximated to the small neuroblastic cells. A similarity to the rods of the retina may be noted. $\times 700$*

CASE 2. AESTHESIONEUROBLASTOMA

A 3-year-old Muganda female presented with a left-sided orbital swelling which had been present for a few months. The patient did not complain of nasal obstruction and no masses were palpable elsewhere. Chest x ray and bone-marrow examination gave normal results. A clinical diagnosis of Burkitt's tumour was made and a biopsy was taken from the orbit. A diagnosis of anaplastic tumour of unknown origin was made at that time and the child was treated empirically with cyclophosphamide. This had no effect after 3 weeks, when the mother and child ran away and have not been seen since.

The diagnosis of aesthesioneuroblastoma was made retrospectively at a slide seminar. The tumour consisted of cells with an epithelial appearance arranged in clumps in a background composed of spindle cells. The spindle cells showed no fibrillary pattern and stains for neural elements were negative. In some clumps the epithelial cells appeared pale and were arranged in an alveolar pattern rather reminiscent of paraganglioma, and elsewhere they were smaller and darker with an organoid arrangement in some parts. Many partially-formed rosettes were seen (Fig. 2, opposite).

Discussion

By far the commonest neoplastic cause of proptosis in childhood in Uganda is Burkitt's lymphoma. The history is much shorter than with many other tumours and is very seldom longer than 3 months. Orbital involvement is seen in about 20 per cent. of children with Burkitt's tumour, but it usually occurs in association with swelling of the maxilla, when it may involve one or both eyes. This association makes the diagnosis fairly obvious clinically. Orbital involvement without clinically apparent swelling of the jaws is seen less frequently and is almost always unilateral. Biopsy is essential for the diagnosis and it

FIG. 2 *Aesthesioneuroblastoma, showing rosette formation and alveolar arrangement of cells. $\times 200$*

is sometimes difficult to obtain satisfactory tissue for standard histological examination (Fig. 3), but touch preparations from very scanty material, even a needle aspiration, will often enable the diagnosis to be confirmed (Fig. 4, overleaf). In the early stages the eye is displaced, but invasion of the orbit is seen only rarely. After prolonged exposure the globe may rupture and in late cases the differentiation from retinoblastoma may be difficult.

The appearance of children with fibrous dysplasia may closely mimic that of Burkitt's

FIG. 3 *Burkitt's lymphoma, showing histiocytes in the tumour which is composed of a homogeneous population of primitive cells. $\times 350$*

FIG. 4 *Touch preparation of Burkitt's lymphoma showing tumour cells with prominent vacuolation in both nuclei and cytoplasm. $\times 900$*

tumour, but x ray studies will usually establish the correct diagnosis. The speckled calcification that occurs in these tumours is virtually never seen in Burkitt's lymphoma.

A more difficult differential diagnosis is that of chloroma. The tendency for acute myelogenous leukaemia to produce orbital swelling has been noted previously (Davies and Owor, 1965). These tumours occur sufficiently frequently to make examination of the bone marrow mandatory in the investigation of any child with proptosis not obviously due to inflammation. The diagnosis of chloroma is sometimes very difficult since the appearance may closely mimic that of histiocytic lymphoma in that the majority of cells are primitive and show abundant pale-staining cytoplasm. If a diligent search is made in such tumours for eosinophilic myelocytes they will usually be found and specific enzyme stains may be used to confirm the diagnosis. The total white count of peripheral blood may be normal in such cases but the marrow almost always shows leukaemia.

Pseudotumours occur most commonly in adults, but three of the twelve examples seen in this 5-year period occurred in children. This fact makes it essential to carry out a biopsy before extirpation is contemplated (Fig. 5).

FIG. 5 *Orbital exenteration carried out for proptosis due to a pseudotumour of the orbit*

Proptosis may be due to involvement by nematode and cestode worms and to various fungus infections, such as histoplasmosis duboisii (Fig. 6). The proportion due to such diseases varies in different parts of Africa. Townsend (1962), for example, records that the commonest cause of proptosis in his practice in South Africa was hydatidosis, but no such case was seen by us in Uganda in 5 years.

FIG. 6 Tissue from the orbit of a 6-year-old girl showing innumerable fungal particles of *H. duboisii*. $\times 200$

Aesthesioneuroblastoma was first described nearly 50 years ago (Berger, Luc, and Richard, 1924) and for some time seems to have remained largely unrecognized. The differential diagnosis from transitional-cell carcinoma is sometimes difficult to make, and it seems likely that a retrospective review of nasal tumours would discover other examples. More recently many reports have been published and it seems likely that it is, in fact, not uncommon (Castro, de la Pava, and Webster, 1969; Skolnik, Massari, and Tenta, 1966). In previously recorded cases the age at onset has ranged from 9 to 79 years, so that our case is the youngest yet recorded by quite a few years. At the age of 3 years the differential diagnosis from metastatic adrenal neuroblastoma has obviously to be considered, but in this case the organoid arrangement which was a marked feature permitted relatively easy distinction. The finding of fibrillary material in the background tissue is useful confirmatory evidence when present, but it is not mandatory for the diagnosis (Hutter, Lewis, Foote, and Tollefsen, 1963). Most of these tumours present with nasal obstruction usually accompanied by epistaxis. Early involvement of the orbit in this case is probably a result of lack of fusion of the intervening bones. The only other case of aesthesioneuroblastoma seen during this review occurred in a 12-year-old child who presented with nasal obstruction in a rather more typical fashion. This tumour probably arises from the basal plate of the olfactory placode but numerous other sites of origin have been suggested.

The origin of the condition, known by many names including retinal anlage tumour (Halpert and Patzer, 1947) and melanotic progenoma (Stowens, 1957), is even more controversial and some would doubt that it is a true neoplasm. The finding of histologically similar tumours in many parts of the body, such as the epididymis (Frank and

Koten, 1967), shoulder (Lurie and Isaacson, 1961), and mediastinum (Misugi, Okajima, Newton, Kemetz, and de Lorimier, 1965), has effectively silenced the claims of dental or retinal epithelium to be the sole progenitor. Most authorities now agree that this is a tumour of primitive neural crest cells which are capable of differentiating towards melanocytic function and towards neuroblastic structure, both of which are seen in this tumour. The term "melanotic neuroectodermal tumour of infancy" seems the most logical one to use. Electron microscopic appearances (Hayward, Fickling, and Lucas, 1965; Misugi and others, 1965; Neustein, 1967) tend to confirm this view, as does the finding that catecholamines may be formed by the tumour (Borello and Gorlin, 1966). However, the statement that this tumour is derived from primitive neural crest cells seems to beg the question why those cells were present at a given site at that time. If the tumour arises in the maxilla it is perhaps reasonable to infer that they might have had odontogenic potential and that cells in the orbit had been destined for the retina, in which case the present patient might reasonably claim to have suffered from the first recorded true retinal anlage tumour, particularly in view of its structure (Fig. 1). The clinical features and therapeutic approach to neoplasia have been well summarized by Allen, Harrison, and Jahrsdoerfer (1969), and it will be sufficient to say here that local removal is almost always effective and that this entity should probably be regarded as a hamartoma rather than a true neoplasm. In spite of repeated summaries of the world literature, the most recent being that of Borello and Gorlin (1966), it seems that one epidemiological feature of this tumour has been overlooked. In 31 of the recorded cases of its occurrence in the maxilla or mandible in which the race of the patient was stated, only one was a Negro (Williams, 1967), and this case was highly atypical clinically and histologically, whereas out of eleven cases in other parts of the body, seven occurred in Negroes.* There is evidence that other tumours of neural crest origin have a very different distribution and frequency in Ugandan Africans and Caucasians. For example, neuroblastoma occurs less frequently (Davies, 1968). At least 50 per cent. of pheochromocytomata occur outside the adrenal (Templeton, 1967), and most melanomata occur on the feet (Lewis, 1967). These embryologically linked anomalies appear worthy of further investigation.

Other derivatives of the neural crest include sympathetic ganglia and nerve sheaths. During the course of this survey, a tumour of each of these structures was found to involve the orbit in children under the age of 3 years. Metastasis from adrenal neuroblastoma to the orbit occurs relatively frequently and all such tumours found at this site should be presumed to be secondary deposits until proved otherwise. There is, however, no theoretical reason why the ciliary ganglion should not be the seat of primary neuroblastoma, but this is difficult to prove. Experience with metastatic neuroblastoma in Uganda is limited since, as stated previously, the incidence of adrenal tumours is lower than in Caucasians (Davies, 1968). By contrast, the incidence in Egypt, where Mortada (1967) has accumulated a considerable number of cases, appears to be quite high. When neuroblastoma does occur in Africans, it does not differ functionally, histologically, or clinically from that seen elsewhere in the world. The differential diagnosis from other causes of orbital swelling such as Burkitt's tumour is assisted by the almost invariable presence of infraorbital ecchymoses which regularly accompany neuroblastoma deposits but which are not seen in patients with Burkitt's tumour. Benign tumours of nerve sheaths are relatively easy to diagnose, but their malignant counterparts excite more controversial views, since the distinctive characteristics seen in benign tumours are often absent. Evidence of palisading is usually not found and the diagnosis is based upon the shape of the spindle cells and the relationship both macroscopically and microscopically to nerve sheaths.

* Present Case 2, and those of Eaton and Ferguson (1956), Lurie and Isaacson (1961), Reyes, Gonzalez-Angulo, and Navarete-Reyna (1964), Frank and Koten (1967), Neustein (1967), and Koudstaal, Oldhoff, Panders, and Hardonk (1968)

Fibrosarcoma displays the same characteristics as in other parts of the body.

The only case of rhabdomyosarcoma seen was of the embryonal variety and did not show cross-striations.

Congenital anomalies seem to show a marked variation in incidence in different parts of the world. In Uganda sacral meningocele is only rarely seen, but nasal myelocele is relatively frequent. It should be noted that, although most of such patients are seen in the first 6 months of life, one child presented with a swelling in the medial side of the orbit at the age of 3 years. In this patient simple excision of the mass of brain tissue appeared curative, and histologically its covering of meninges appeared complete, arguing that connection with the subarachnoid space had been obliterated.

Orbital haemangioma is a common cause of proptosis in most parts of the world and its rarity in this series is puzzling since it is seen elsewhere in the body quite frequently.

Summary

The diagnosis of proptosis due to orbital tumour in a series of sixty cases in Ugandan children is analysed. Nearly half of these cases were due to Burkitt's lymphoma but other conditions seen fairly frequently included chloroma, fibrous dysplasia, and anterior myelocele. Two cases appear to be unique, in that neither aesthesioneuroblastoma nor retinal anlage tumour has been reported previously in the orbit.

Thanks are due to Dr. L. B. Thomas and Dr. R. V. P. Hutter who kindly confirmed the diagnosis in Case 2. The Kampala Cancer Registry, from which this study derives, is supported by the Cancer Research Campaign.

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