



Cancer Genetics Gazette

This gazette is sent to you from the **Familial Cancer Unit of the South Australian
Familial Cancer Service**

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Welcome to the first issue of the Cancer Genetics Gazette for 2004. This newsletter aims to provide specialist clinicians with up-to-date information about familial cancer.

Please feel free send suggestions for future topics as well as feedback about any articles that feature in the Cancer Genetics Gazette to:

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The mailing list of clinicians receiving this newsletter has been generated from the Register of Practitioners in the South Australian Government Gazette. Please contact Clara Tait should you not wish to receive this newsletter, if you prefer to receive it electronically or should your contact details change.

This newsletter features an article about **Ophthalmic Manifestations of Familial Tumour Syndromes** by Dr James Meucke.

Ophthalmic Manifestations of Familial Tumour Syndromes

A number of familial tumour syndromes have important ophthalmic associations which may be threatening to the sight, the eye or the body. The majority of these ophthalmic associations are themselves benign or cancerous tumours, and may be seen within the orbital tissue, on the eyelids or surface of the eye or within the eye itself. It is important for health care professionals treating patients with such syndromes to keep in mind the ophthalmic associations and to consider referral to an ophthalmologist trained in the current management of these conditions.

Orbital tumours

Neurofibromatosis Type 1 (NF1)

NF type 1 is the commonest of the phakomatoses and has a constellation of ophthalmic associations. Hamartomatous Lisch nodules are eventually seen in almost all patients, are an important diagnostic criterium, but harmless to the patient. Plexiform neurofibroma of the upper eyelid is rare but points to an increased risk of glaucoma. The most important manifestation is optic glioma (pilocytic astrocytoma) and is the primary reason for regular ophthalmic review throughout childhood. Fortunately, optic gliomas often behave as stable hamartomatous lesions and may be discovered as an incidental finding on neuroimaging. Gliomas diagnosed in early childhood are usually more aggressive with rapid appearance of proptosis and visual compromise due to compression within the optic nerve or chiasm. Chemotherapy with intravenous carboplatin given monthly results in

stabilization of the lesion and avoidance of harmful radiotherapy in the majority of patients. Autosomal dominant inheritance indicates a need for screening of at-risk family members.

Eyelid tumours

Basal Cell Naevus Syndrome (BCNS)

Multiple naevoid basal cell carcinomas involving the skin of the eyelids and periocular structures are one of the key features of this autosomal dominant syndrome. The BCCs usually begin in adolescence and can grow to extensively involve the periocular and orbital tissues. Referral for regular ophthalmic review commencing in late childhood is indicated in order to detect eyelid tumours at the earliest stage. Protection from the sun commencing early in life is advisable. Conservative treatment such as cryotherapy may be possible for small lesions, but eventually margin-controlled excision of BCCs with reconstructive surgery may become necessary. Other ophthalmic associations include uveal colobomas and glaucoma. Screening of at-risk family members is recommended with early dermatology review and long term follow up of patients with BCNS.

Muir Torre Syndrome (MTS)

Multiple benign sebaceous gland adenomas involving the skin of the eyelids should raise suspicion of this rare autosomal dominant syndrome. There is a risk of highly malignant sebaceous gland carcinomas of the eyelids. The carcinomas may be multicentric and can show infiltrative growth with orbital and systemic spread. Radical surgery may be necessary. Regular ophthalmic review is recommended in patients with MTS. Screening of at-risk family members and long term medical follow up of patients with MTS is necessary in view of the significant associated risk of gastrointestinal malignancy.

Ocular Surface Tumours

Organoid Naevus Syndrome (ONS)

Complex epibulbar choristomas are benign ocular surface lesions that may be seen in association with linear naevus sebaceous of the skin in ONS. They are stable, pose no risk to the eye, rarely constitute a cosmetic deformity and treatment is

usually unnecessary. Long term follow up of naevi is indicated due to the risk of malignant transformation to BCCs. Other ophthalmic associations include eyelid and uveal colobomas. Sporadic inheritance means that family screening is unnecessary. The risk of neurological abnormalities with seizures and mental retardation in children with linear naevus sebaceous should prompt early referral to a paediatrician.

Intraocular tumours

Sturge Weber Syndrome (SWS)

SWS is readily identified by the bright red vascular malformation involving the facial skin within the first (\pm second) division of the trigeminal nerve (port wine stain or naevus flammeus). This is present at birth and remains relatively stable throughout childhood. It is often associated with a vascular malformation involving the ipsilateral tissues of the ocular surface. These findings should immediately raise the suspicion of associated glaucoma, which is seen in up to 70% of patients with SWS. Prompt referral to an ophthalmologist is indicated. A vascular malformation involves the ipsilateral choroid in 40% of patients, giving the classical "tomato ketchup fundus". Choroidal "tumours" have a high risk of subretinal exudation with resulting retinal detachment and loss of vision or even eye. Regular fundal examination is necessary in these patients in order to detect leakage and treat early with lens sparing external beam radiotherapy. The risk of an associated vascular malformation involving the ipsilateral meninges should prompt early referral to a paediatrician. Sporadic inheritance means that family screening is unnecessary.

Von Hippel Lindau Syndrome (VHLS)

There are no external clues to VHLS, but a family history of spinal or cerebellar haemangioblastoma or of pheochromocytoma must raise the suspicion of this phakomatosis. All patients with a diagnosis of VHLS require annual fundal examination by an ophthalmologist in order to detect retinal capillary haemangioblastomas which are eventually seen in over 80% of patients. These benign vascular lesions have a high risk of subretinal exudation with resulting retinal detachment and loss of vision or even eye. If detected whilst still small, they are

usually treatable with retinal laser or cryotherapy. Autosomal dominant inheritance indicates a need for screening of at-risk family members. Fundal screening of children of patients with VHLS should begin at the age of three. Fortunately, genetic testing of the VHL1 gene can detect the responsible mutation in 90% of patients and can be used to exclude family members without the mutation from a lifetime of ophthalmic and systemic screening. Long term medical follow up of patients with VHLS or with the VHL1 mutation is necessary, in view of the high risk of systemic malignancies such as renal cell carcinoma.

Tuberous Sclerosis (TS)

Fortunately the ophthalmic manifestations of TS are usually harmless and include angiofibromas of the eyelid skin and hamartomas of the retina. The hamartomas are seen in up to 50% of patients. They may rarely show aggressive local growth with loss of vision and so regular fundal examination by an ophthalmologist is indicated throughout childhood. Autosomal dominant inheritance indicates a need for screening of at-risk family members. The risk of cerebral hamartomas with seizures and mental retardation in children with facial angiofibromas should prompt early referral to a paediatrician.

Familial Adenomatous Polyposis (FAP)

One of the many extra-colonic markers of FAP are familial hamartomas of the retinal pigment epithelium - FHRPEs (also known as atypical congenital hypertrophy of the RPE - CHRPEs). These retinal lesions are completely benign but may be seen in up to 70% of patients with FAP. Since the advent of genetic mutation testing for FAP, the use of these lesions as a screening tool has become less important. In the 10% of patients where the responsible mutation is not detected, FHRPEs can be used for screening of at-risk relatives - the presence of lesions in family members is an indication for colonoscopy.

Dr. James Muecke is a visiting ophthalmologist at the Royal Adelaide and Women's and Children's Hospitals. He specializes in tumours of the eyelid, ocular surface and intraocular structures. Please visit his website www.eyedoctors.com.au for more information about ophthalmic tumours.

Letter to the Editor

Dear Editor,

Re Surgery in Familial Polyposis

The article in the last Cancer Genetics Gazette suggested that ileoanal pouch was the "gold standard" in surgery for FAP. The decision on which surgical option to employ is not this straightforward.

There are 3 surgical options. Proctocolectomy and end ileostomy (seldom indicated), proctocolectomy and ileoanal pouch (pouch), and total colectomy and ileorectal anastomosis (IRA). In advising patients about these options the following points need to be addressed.

- 1) Death in FAP is mostly associated with duodenal carcinoma and desmoid disease (no difference between pouch and IRA).
- 2) An ileoanal pouch is associated with a 1% impotence, retrograde ejaculation, or urinary incontinence rate in males and a 50% reduction in fecundity in women.
- 3) If a pouch cannot be formed there is a real chance of having to form a permanent ileostomy at the original surgery.
- 4) The pouch failure rate is 15%.
- 5) The risk of rectal carcinoma after IRA is 8% at 50 years and 30% at 60 years (St Marks/Cleveland data personal communication)
- 6) The functional results of IRA are superior to a pouch.
- 7) Pouch adenomatous polyps are being increasingly encountered.

Patients with mutation 1309 should be offered a pouch even if there are no rectal polyps. In other patients without relative rectal sparing or who are older, a pouch is probably the best choice. For younger patients with relative rectal sparing (<20 polyps) an IRA with rectal surveillance is a very reasonable alternative.

Patients must be offered informed consent and IRA is often their choice.

Jim Sweeney
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Genetic testing for Familial Cancer in South Australia

The South Australian Familial Cancer Service has been running for six years. The first condition in which genetic testing was offered was familial adenomatous polyposis. The repertoire of genes that can be tested has increased substantially and includes the genes responsible for the following conditions:

- ❖ Familial breast and ovarian cancer (BRCA1 and BRCA2 genes).
- ❖ Familial adenomatous polyposis (APC gene).
- ❖ Hereditary non-polyposis colon cancer (MLH1, MSH2, MSH6, and PMS2 genes).
- ❖ Cowden syndrome (PTEN gene).
- ❖ Hereditary retinoblastoma (RB1 gene).
- ❖ Hippel-Lindau syndrome (VHL gene).
- ❖ Hereditary schwannomatosis (NF2 gene).
- ❖ Multiple endocrine neoplasia type 2 (RET gene).

Testing these genes is performed in South Australian laboratories but pre-test genetic counselling and consent must be arranged through a familial cancer clinic. Clinics are held at major teaching hospitals and in regional centres. All referrals and clinical enquiries should be addressed to the Familial Cancer Unit at the Women's & Children's Hospital (Telephone 08-8161 6995).

Audit group meetings

In South Australia the main method for fostering multi-disciplinary management has been quarterly meetings of clinical, genetic, and laboratory experts. At these Audit Group meetings we review the indications for genetic testing, the outcome of recent laboratory studies, and the appropriate management of those shown to carry an abnormal gene. There are separate Audit Group meetings for familial breast & ovarian cancer, for familial colorectal cancer (including HNPCC), and familial neuro- & ocular-oncology (RB, VHL, NF2).

This model has worked well and has helped make the South Australian service among the best in the country. The Audit Group meetings are open to all professionals with involvement in the relevant cancers. If you would like to attend or to receive notices of meetings & minutes, please let me know.

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