

Neurology 101 – New ideas about NCM, neurologic complications and treatment

Presentation Dr. Yasmin Khakoo

Nevus Outreach Conference July 2018

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Notification: this report is based on my personal notes and pictures made from the presentation. Though I believe it's quite an accurate report of the presentation, I'm not responsible for misinterpretations or translation errors.

Dr. Khakoo is a strong advocate of doing more tests when a child is born. In the first year of life she recommends an eye exam, audiogram, and MRO is head and spine. Also, she would like children to be seen by a neurologist twice during the first year. Dr. Karin Malin (neuropsychologist) adds to also perform neuropsychological tests when a child has learning problems or experiences other problems at school. Neuropsychological tests are specifically designed tasks used to measure a psychological function known to be linked to a particular brain structure or pathway, which might not function very well because of NCM.

MRI techniques have improved since the past 20 years and more neurological symptoms in a range from severe to less severe are linked to neurological complications of CMN.

The recommendations for making a baseline MRI vary per country. Dr. Veronica Kinsler (UK) advises to make an MRIs when there are two or more CMN. Dr. Sven Kregel recommends an MRI when there are multiple satellites or a GCMN. Some countries don't recommend an early MRI.

This last year Dr. Yasmin Khakoo has seen four patients with a single MCMN with neurological involvement and therefore recommends everyone with MCMN or more/bigger CMN to have an MRI made. Preferably before 6 months of age, but even later before 12 months will still be helpful to have as a baseline.

Dr. Barkovich has received more than 200 MRI's and his findings will be published in the journal of radiology. His work will be taken over by someone else in the future.

For better interpretation of the MRI, Dr. Khakoo advises to include a clinician's report, an EEG report, a pathology report and a picture of the child.

Presentation:

A publication once in the journal of clinical oncology stated "NCM is fatal...", which Dr. Khakoo says is not true, but it has become a myth going around. The definition of NCM is a rare neurocutaneous syndrome defined by the presence of large and/or multiple congenital cutaneous nevi and melanocytes in the CNS. In 2005 Dr. Marghoob reviewed 379 patients with LCMN and found the incidence of asymptomatic NCM 4.8%.

NCM is defined as:

When there's a large CMN (>20 cm) and/or multiple (>3) congenital melanocytic nevi (CMN) with meningeal melano(cyto)sis or melanoma. There is no skin melanoma except when meningeal lesions

are benign, also no meningeal melanoma except when skin lesions are benign. Distinguish metastatic melanoma from NCM, it's not the same.

LCMN: 1/20.000

NCM: 1/200.000

M=F

Most patients become symptomatic by the age of 2 years, 70% by 5 years and there are reports of patients becoming symptomatic in 2nd or 3rd decade. 12% of all patients with LCMN have NCM; 4.8% of patients remain asymptomatic (Agero et al 2005)

Embryology

Melanocytes: neural crest, migrate throughout the body including leptomeninges

Nevi: are transformed melanocytes which arrest along the path

NCM may be a marker for abnormal neuronal migration

Risk factors for NCM

- Size or LCMN: Larger nevi associated with increased risk of NCM
- Number of satellite nevi: Patients with 20 or more satellite nevi are at risk for NCM and should have screening MRI (Marghoob et al 2004)
- Location: Originally felt that posterior midline LCMN (PML) were associated with high risk of NCM. Current thinking: patients with posterior midline rarely have NCM.

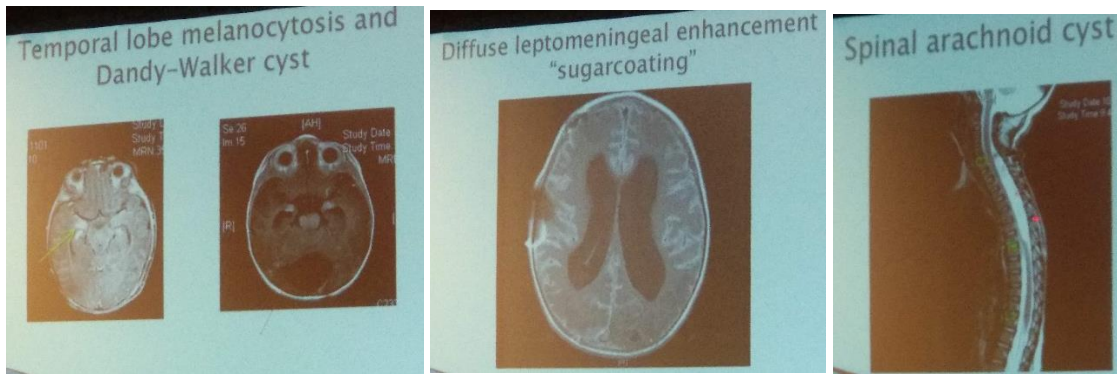
One of the symptoms can be hydrocephalus. Signs and symptoms are headaches (irritability, head banging in pre-verbal), enlarging head circumference, bulging fontanel (soft spot), morning nausea and vomiting, limited up gaze (Sun setting eyes), diplopia (double vision) and lower extremity spasticity (baby crosses legs when lifted).

Seizures are electrical storms in the brain, caused by irritants on the surface of the brain (blood, infection, tumors). In NCM neurons (brain cells) may have migrated differently resulting in seizures. Evaluation may include EEG, prolonged EEG. Dr. Khakoo mentioned a case where a boy didn't hear a door slamming and the audiogram showed no hearing loss. Apparently the boy was having small seizures and therefore missing the sound. There are various treatments for seizures.

Cranial nerve symptoms/signs may have diminished hearing because of NCM on auditory nerves or cochlea. Screening audiogram is recommended for all patients. Sign language can help the patient. All patients should have baseline eye exam.

Developmental/Behavior issues may result from chronic neurologic conditions (seizures, hydrocephalus etc.) or psychological effects of having LCMN or early intervention for children under 3 yrs. The child may need psychological support as it gets older. Certain seizure medications may be helpful for treating behavioral issues as well.

Spinal nerve root and cord compression (from arachnoid cyst or leptomeningeal nodules) can be delayed motor milestones or toe walking (myelopathy, caused by cyst on spine or hydrocephalus), delay in toilet training or back pain. Treatment can be steroids or surgical decompression



Source:

<https://www.ncbi.nlm.nih.gov/pubmed/22469364>

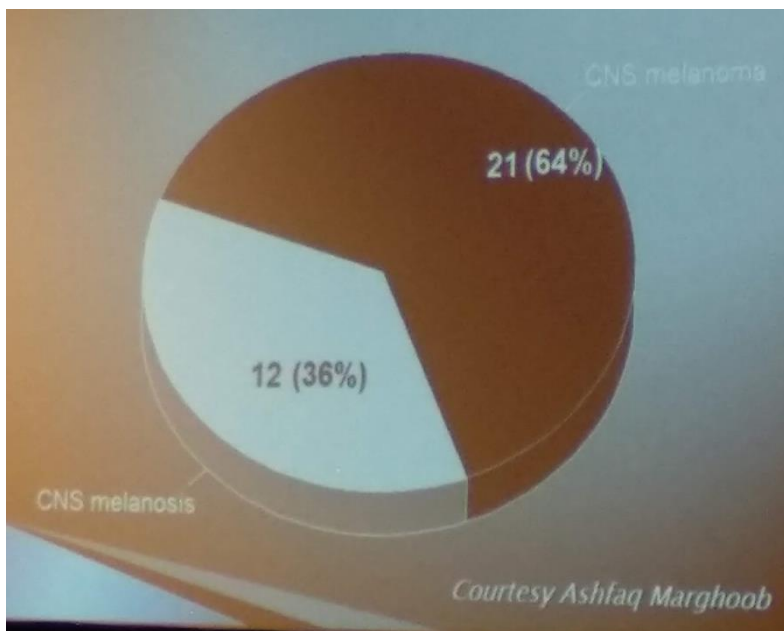
Spectrum of central nervous system abnormalities in neurocutaneous melanocytosis.

Ramaswamy V1, Delaney H, Haque S, Marghoob A, Khakoo Y.

Study 33 cases NCM or melanoma?

Wit is CNS melanosis

Bruin is CNS melanoma



CNS melanoma treatment options

- Interferon alpha and IL-2 have not been effective
- Temozolomide oral chemotherapy may help prolong survival
- Platinum based IV chemotherapy may also prolong survival
- Ipilumimab / nivolumab
- Intrathecal radio-immunotherapy may be more specific

Future directions

- Targeted therapy: MEK / Ras / BRAF pathway?
- Other pathways

- Methylation array, RNASeq, cfDNA
- Learning more about incidence or spinal cysts
- Raising awareness in the medical community

Thinking of KRAS a drug used in lung cancer.

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