An update on congenital melanocytic naevi in children

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CLASSIFICATION OF CMN

The classification of CMN has recently been unified with that of other congenital naevi (epidermal, connective tissue). This is based on clinical phenotype, histology (undifferentiable currently for CMN) and genotype:

Clinical phenotype:
1. Cutaneous only – single, or multiple (more than one lesion at birth)
2. With extracutaneous features – then termed CMN syndrome

Genotype:
1. NRAS mutation positive
2. Other causative mutation (would need to be shown in more than one lesion from the same patient, no other causative mutations yet published)

To further refine the clinical phenotypic groups the most recent classification proposed to define the severity of the cutaneous phenotype is as follows:

CMN projected adult size categories: small (<1.5 cm); medium (M1: 1.5-10 cm, M2: >10-20 cm); large (L1: >20-30 cm, L2: >30-40 cm); and giant (G1: >40-60 cm, G2: >60 cm)

Total number of naevi in the first year of life: 0, 1 to 20, 21 to 50, 51 or more

Additional descriptors of CMN: localization, colour heterogeneity, surface rugosity, hypertrichosis (all none, moderate, marked), presence of nodules (none, scattered, extensive)

In the author’s own practice however the terms relating to size are not used (only measurement), and in particular ‘giant’ is avoided as it is often disliked by families, and nor is the term ‘satellite’ naevi as these are true congenital naevi in their own right, not an offshoot of the largest lesion. Also in the author’s practice the total number of naevi is categorized as 0-10, 11-20, 21-50, 51-100, 101-200, and >200, because many severely affected children are seen. Lastly the author also registers whether the lesions are clinically stable or not (ie producing new nodules), and whether the patient is developing new naevi.

GENETICS OF CMN

In 1987 Happle predicted that CMN syndrome (under the term neurocutaneous melanosis) would be one of various dermatological conditions caused by a lethal mutation surviving by mosaicism. The first contributions to the molecular genetics of CMN were descriptions of mutations in single CMN, or in single lesions from any one patient. These studies described mutations in BRAF, NRAS, MC1R, TP53 and GNAQ. As with all single lesions and indeed with the study of genetics of tumours the difficult lies in assigning their order in the pathogenesis of that lesion. As a result a study was performed to look at more than one lesion from the skin, and from neurological tissue from the same patients. This found that in 80% of cases tested there was conservation of codon 61 mutations in NRAS in different lesions from the same patient, which implies that this mutation is causative. The mutations were absent from blood, proving Happle’s original theory. This condition is therefore a mosaic RASopathy in at least 80% of cases.

SINGLE CMN

A distinction is made between single CMN of any size and multiple CMN (more than one at birth) because extracutaneous abnormalities have not so far been shown in any patient with a single lesion, independent of size or site. While this could still be reported, the risk of extracutaneous problems is clearly low. There is also a good genetic correlate for this observation, as a single CMN suggests a mutation in the embryo affecting only one area of skin, and therefore presumably at a time where the naevus cell lineage was already fate restricted to that one area.
Single CMN are still on the basis of pathogenesis likely to carry an increased risk of melanoma compared to normal skin, but this appears to be very low.\textsuperscript{17-21} These lesions are therefore not routinely excised for reasons of malignancy risk in the author’s practice.\textsuperscript{21} They can however be excised for cosmetic lesions if wished by the patient and if technically feasible.

Management of single CMN in the author’s practice therefore is detailed examination of the patient to check there are no other CMN no matter how small, full physical examination and neurodevelopmental assessment, photography of the lesion, contact made with the patient support group, contact with the plastic surgery team if wished, and then discharge from the Dermatology clinic unless the single lesion is of more than 20cm projected adult size (rare). If the clinical assessment was normal no routine MRI of the CNS is performed independent of the size or site of the lesion. The patient knows they can be referred back to our clinic at short notice if they have any concerns.

The one caveat to this is in the case where the single CMN is associated with other types of pigmented lesion, or with other physical problems, CMN are sometimes the presenting feature of other conditions, most commonly in the author’s practice neurofibromatosis type 1. These patients should therefore be kept under review until the situation becomes clearer.

**MULTIPLE CMN (MORE THAN ONE LESION AT BIRTH)**

Individuals with multiple CMN carry a risk of extracutaneous abnormalities. In 2008 we published guidelines suggesting that all children more than one CMN at birth should have a routine screening MRI in the first 6 months of life, but single lesions even large or overlying the CNS should not. These guidelines have recently been reviewed and we have found that although the percentage of scans performed has dropped significantly, the percentage of abnormalities detected has not (remains around 20%).\textsuperscript{22} Therefore we can assume that these guidelines have not led us to miss any or certainly not a large number of abnormalities. On the basis of clinical phenotype however we are not currently able to refine these guidelines further. Although there is a general association between the severity of the cutaneous phenotype and the chance of neurological abnormalities,\textsuperscript{17-19,21-24} this is far from perfect, and individuals with two CMN can still be found to have important lesions on scan.\textsuperscript{19,24}

**CMN SYNDROME**

This term describes the association of CMN and extracutaneous features. These include neurological abnormalities, characteristic facial features, and more recently discovered rarely a hypophospha-
The scan does not need to be repeated routinely, and these lesions are not malignant so do not lead of themselves to a fatal outcome even if symptomatic.

3. **All other findings** on MRI have to be treated on an individual basis – approximately 10%. These findings include benign brain tumours, congenital malformations such as Dandy-Walker, leptomeningeal disease either focal or diffuse, and mostly these are also associated with intraparenchymal melanosis as described above. This group as a whole have a much more guarded prognosis, as many require neurosurgery, many lesions are unique to that patient, and many (but not all) children are neurologically abnormal. These patients require referral to the paediatric neurology and neurosurgery teams, for assessment and follow up, and repeat scanning is the norm until the behaviour of individual lesions is clear. Diffuse leptomeningeal disease requires a particular mention as this frequently behaves as melanoma, and repeat scans are required at short intervals (weeks or months) until stability is established or malignancy is diagnosed.

**CHARACTERISTIC FACIAL FEATURES IN ASSOCIATION WITH CMN**

Children with CMN have been found in one cohort to have characteristic facial features. Their faces are not strikingly dysmorphic, however they do have a common face shared with other children with the same condition. The facial phenotype does not so far appear to be connected to the severity of the cutaneous phenotype, or to the presence of the neurological phenotype, but larger studies are underway to examine these questions. At least three characteristic facial features were seen in 70% of the children studied, and the possible facial features are as follows: a wide or prominent forehead, hypertelorism, eyebrow variants, periorbital fullness, small/short nose, narrow nasal bridge, anteverted nares, broad nasal tip, broad or round face, full cheeks, prominent pre-maxilla, open mouth appearance, prominent everted lower lip, and prominent or long philtrum. Characteristic facial features are seen in a variety of genetic disorders where the underlying abnormality is mosaic, for example Pallister-Killian syndrome, and mosaic Cornelia de Lange syndrome. **The RAS pathway germline conditions all also** are therefore known to influence facial development.

**MELANOMA IN CMN PATIENTS**

For single CMN and melanoma see above. Individuals with CMN have a risk of developing melanoma, which is thought to peak in childhood, and although it is not inconceivable that this is due to publishing bias, the author’s impression is that there is a peak in childhood due to the complex neurological phenotypes carrying a significant risk of malignant transformation. For individuals with multiple CMN or CMN syndrome the risk of melanoma is a genetic risk to that individual, and there is no evidence thus far that UV exposure has anything to do with the risk of melanoma development. Sensible UV protection precautions are therefore a good idea as for all children, but over-zealous UV protection is not advised.

Melanoma arising in the skin of children with CMN, particularly those with severe cutaneous phenotypes, is difficult to detect. This is partly because CMN are often highly heterogeneous making detection physically difficult, and partly because of the confounding problem of benign proliferative nodules. Proliferative nodules are common in severe phenotypes, and come in many phenotypic guises. As a general rule, the author deals with new nodules by having open access to clinics at short notice for a new lump in a CMN (patient usually seen within two weeks of reporting the issue), a photograph is taken with a scale, the patient is examined thoroughly, and if everything else is normal the nodule is reviewed within four weeks. If the nodule has grown or changed markedly within that time it will be resected. The vast majority however do not change, but stabilize. This avoids continuous resections in patients who produce many nodules, but judgement obviously has to be exerted for individual cases.

At least half the cases of melanoma in children with CMN arise as a primary in the CNS, and in the author’s experience it is much more common in the CNS than in the skin. Melanoma in the CNS usually presents with hydrocephalus before the fontanelles have closed, or raised intracranial pressure if afterwards. It can either appear as a solid intraparenchymal tumour, sometimes but not necessarily connected to the leptomeninges, or as leptomeningeal disease. While the solid intraparenchymal tumour will look different from congenital neurological disease in this condition, with malignant radiological features, the leptomeningeal disease does not necessarily look different initially. Indeed, often very early in the process no leptomeningeal disease is detectable on MRI, due to the limits of resolution of scanning, and only becomes apparent after some weeks. In the situation of acute onset of hydrocephalus or raised intracranial pressure with no other apparent cause therefore it is reasonable to assume that leptomeningeal disease is leading to obstruction of circulation of cerebrospinal fluid. The treatment for this in the short-term is ventriculo-peritoneal shunting, which improves the situation symptomatically. However, follow up scanning within a month is advocated to look for radiological progression, as this is an important sign of malignant disease. If progression is shown a leptomeningeal biopsy (or biopsy of a solid tumour) is the next step.
Biopsy of CNS tissue for melanoma is fraught with the same problems as cutaneous melanoma in CMN tissue. Histology is notoriously difficult, and should be reviewed by at least two individuals with experience in the field. More recently, published and unpublished data from our lab on NRAS mutation testing has been shown to be useful, in that loss of the normal allele of NRAS (ie a progression from heterozygous NRAS mutation to homozygous mutation) can occur in melanoma. The reverse however is not true, as melanoma can be present with only a heterozygous NRAS mutation, although other mutations are usually seen. Groundbreaking research on the utility of array comparative genomic hybridization in differentiating melanoma in CMN from benign proliferative nodules has been confirmed in our laboratory in CNS malignancy as well as in the skin (unpublished data). Our current practice therefore is to do NRAS sequencing and array CGH on any tissue suspected of malignant transformation. In the author’s opinion there is no place for lumbar puncture and histology of melanocytic cells in the cerebrospinal fluid, as these results are very difficult to interpret, and cells will be present in anyone with leptomeningeal disease, benign or malignant.

Melanoma can also rarely arise within other tissues, and other non-melanoma tumours (in particular rhabdomyosarcoma) have also been rarely described in individuals with CMN. Any unusual mass lesion in children with CMN should therefore be taken seriously and investigated thoroughly.

As a general principal, although rare, where melanoma does arise in CMN patients it is extremely difficult or impossible to treat, with almost every proven case being fatal within 6-12 months from diagnosis. This is almost certainly due to the genetic drivers involved in this disease, but will also be confounded by difficulty of detection. New trials of new drug therapies are being trialled in the author’s institution for melanoma in these patients. Prophylactic surgical resection of large areas of multiple CMN has not been shown to reduce the malignancy risk in this condition, probably for the genetic reasons given above, and because the majority of cases arise in the CNS. This does not preclude the judicious use of surgery for cosmetic reasons where deemed appropriate by the family and clinicians.

REFERENCES


De complete literatuurlijst is, vanaf drie weken na publicatie in dit tijdschrift, te vinden op www.huidarts.info.
SUMMARY
The classification of congenital melanocytic naevi (CMN) mirrors that of other congenital naevi. Hence CMN can be single or multiple, defined as two or more lesions at birth, whereas CMN syndrome is the association of CMN with extracutaneous features. Extracutaneous features described are characteristic facies, congenital neurological abnormalities, and very rarely abnormal bony metabolism. The term CMN syndrome has replaced the term neurocutaneous melanosis, due to the broad spectrum of neurological features described.

A screening MRI scan of the CNS in the first year of life (ideally under 6 months), looking for congenital neurological abnormalities, has been shown to be the best predictor of clinical outcome in infants born with multiple CMN, independent of size or site. These results therefore dictate clinical management. This should be differentiated from MRI in any CMN patient with new neurological symptoms, to look for primary CNS melanoma, at least as common as cutaneous melanoma. Overall rates of malignancy are low (approximately 2%), however the most severely affected children have a substantial risk (approximately 10% in those with CMN greater than 40cm projected adult size).

The genetic basis of multiple CMN and CMN syndrome has been established in the majority of cases (approximately 80%). This condition is a mosaic RASopathy, due to post-zygotic mutations in the gene NRAS. NRAS controls many important inter-cellular signalling pathways, and is already known to be involved in the pathogenesis of melanoma in the normal population. This explains the predisposition to melanoma in individuals with CMN, however further mutations are required to progress from the naevus to malignancy.

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Tijdens een zwangerschap kunnen zich talrijke huidmanifestaties voordoen. Het is belangrijk deze frequente problematiek goed te herkennen. We moeten goed het onderscheid kunnen maken tussen deze die een strikte opvolging en behandeling vergen, en deze die eerder gewoon een geruststelling van de moeder vereisen.

De cutane manifestaties van de zwangere vrouw worden gewoonlijk in vijf groepen onderverdeeld:
1. Fysiologische veranderingen van de huid, door de hormonale veranderingen, het grotere intra-vasculaire volume en door de compressie uitgaand van de zwangere uterus
2. Specifieke dermatosen van de zwangerschap, waarop we verder zullen ingaan
3. Huidinfecties die de maternofoetale prognose kunnen verslechtern
4. Uiteenlopende huidziekten die kunnen verergeren tijdens een zwangerschap en/of de gezondheid van de foetus kunnen aantasten
5. Bijwerkingen van lokale behandelingen van de huid, en het risico voor de foetus van sommige moleculen

De reden waarom huidziekten relatief vaak voorkomen bij zwangerschap, is te zoeken bij een shift van een predominant T-helper 1-lymfocyt fenotype naar een T-helper 2-fenotype. Deze transitie maakt dat er geen rejectie is van de foetus, omdat de placenta een ander cytokineprofiel produceert. De hoeveelheden interleukine-12 en interferon-γ dalen, en de hoeveelheden interleukine-4 en interleukine-10 nemen toe. Dit maakt dat de vrouw meer vatbaar is voor auto-immunaandoeningen, en vatbaarder voor infecties omdat de celgemedieerde immuniteit afneemt.

De ervaring leert dat ongeveer 50% van de vrouwen een exacerbatie van een frequent voorkomende inflammatoire huidziekte (psoriasis, eczeem, acne, rosacea) of een huidinfectie vertonen. Ongeveer 30-50% presenteert zich met één van de drie specifieke zwangerschapsdermatosen: pemphigus gestationis, polymorfe eruptie van de zwangerschap, of de atopische eruptie van de zwangerschap.

Impetigo herpetiformis is een andere zeldzame dermatose die in de zwangerschap voorkomt, maar soms ook er buiten. Daarom wordt ze niet bij de specifieke zwangerschapsdermatosen geklasseerd, hoewel ze het meest voorkomt in het laatste trimester, met snel herstel in de post-partumperiode. De benaming is misleidend, want er is geen enkele oorzake-