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Approach to Abnormalities in Head Shape and Size Part 3: Macrocephaly

Developed by Lindsey Logan and Claire McNiven with Dr. Melanie Lewis, Dr. Lauren Redgate, and Dr. Peter Gill for PedsCases.com.
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Introduction:

Lindsey: Okay, we are back for part 3 of our series on head shape and size.

Claire: My name is Claire McNiven, a pediatrics resident at the University of Alberta.

Lindsey: And I am Lindsey Logan, a pediatric neurology resident in Toronto.

Claire: We want to thank our mentors who helped us develop and edit this podcast, Dr. Peter Gill from SickKids, Dr. Melanie Lewis from the Stollery Children's hospital, and Dr. Lauren Redgate, a pediatrician in Calgary, Alberta.

Lindsey: In our first podcast we reviewed head growth and skull anatomy. In Part 2, we reviewed an approach to abnormal head shape.

Claire: Again, If you need a refresher, feel free to rewind to parts 1 and 2, where we cover all of that in detail!

Lindsey: Today, our podcast is all about head size, specifically we cover heads that are too big. Stay tuned for our fourth and final podcast, where we move on to talk about heads that are small.

The objectives for today's podcast are the following:

1. Determine the differential diagnosis for children presenting with large heads.
2. Review important points on history and physical examinations which will help elucidate the etiology of the macrocephaly.
3. And finally, Discuss an approach to investigation and management of children presenting with macrocephaly

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Definition of Macrocephaly

Claire: “Macro” means “large” and “cephaly” means “head” in Latin. So macrocephaly literally means large head.

Lindsey: This is a little different than the descriptive term “bigheaded”, which basically just means big ego.

Claire: Yes, and macrocephaly, again meaning large head, is different from megalencephaly, which is an increase in the size of the brain. Megalencephaly implies macrocephaly, as the head would need to be large to accommodate a large brain, but macrocephaly does not imply megalencephaly.

Lindsey: In simpler terms, having a large brain will make your head size large, but having a large head size does not mean your brain is too large.

Claire: Macrocephaly is defined as head circumference greater than 2 standard deviations above the mean for the age and sex of the patient. 2 standard deviations above the mean is the same as the 97th percentile.

Lindsey: Before we discuss the differential for macrocephaly, let’s start with a case!

A 2-month-old girl, let’s name her Lucy, is referred to your clinic by a family doctor. Her head circumference was measured at the 75th percentile at birth, but at her recent visit to the family doctor’s office her head circumference was measured at the 97th percentile. You have been asked to see her regarding potential macrocephaly. What do you think?

Claire: Before we can decide if this is abnormal, we must first determine what normal is. Both in terms of the general population’s head sizes, which are denoted by the percentiles, and our patient’s normal: in terms of her other growth parameters, as well as her other family members head size.

Lindsey: We also want to have an idea of the possible things that could be causing Lucy’s head to be large. Let’s take a step back and discuss the differential.

Objective 1: Differential Diagnosis of macrocephaly

Claire: The first step in the approach to macrocephaly is to organize the differential by potential causes. Anything that is inside the head may contribute to an increased head size.

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Lindsey: Therefore, the differential includes conditions that increase brain size, conditions that increase the amount of cerebrospinal fluid (also known as CSF), conditions that increase the amount of blood in the head, the amount of bone in the head, and mass lesions which occupy space in the head.

Claire: Conditions that increase the size of the brain may be divided into anatomic or metabolic subcategories. Some common anatomic causes of increased brain size include benign familial megalencephaly, autism spectrum disorder, achondroplasia, and neurocutaneous disorders such as neurofibromatosis and tuberous sclerosis, just to name a few. Possible metabolic causes include organic acidemias, like methylmalonic acidemia, and lysosomal storage disorders.

Lindsey: Conditions that increase the amount of CSF may also be termed hydrocephalus. Hydrocephalus essentially means fluid in the brain. This can be caused by increased production of cerebrospinal fluid, or decreased resorption.

Claire: Most commonly, decreased resorption is because of a blockage between the region of the brain where CSF is produced and the areas around the brain where it is reabsorbed into the venous sinuses.

Lindsey: Yes, CSF is produced in the choroid plexus on the floor of the lateral ventricles. It then circulates around the brain into the subarachnoid space and becomes reabsorbed into the cerebral sinuses through arachnoid granulations. Claire, I have a pop quiz question for you! Can you remember how many mL of cerebrospinal fluid are generated each hour?

Claire: I can look it up! Hmmm, 25 mL of CSF is produced every hour in adult brains!

Lindsey: Exactly, and we only have about 5 times that, or 125mL, in circulation at a given time. So anything blocking the cycle of reabsorption can pretty quickly lead to increased accumulation and pressure from this excessive fluid. Of course, if the blockage is only partial, it takes longer for hydrocephalus to develop, but it follows the same reasoning.

What do you think happens to infant's heads when they have increased CSF?

Claire: Well, because of the sutures and fontanelles, any pressure caused by increasing the amount of CSF in the skull would cause the head to expand and grow very rapidly!

Lindsey: Yes! The sutures may also "splay" out and fontanelle can become full or bulging.

Claire: There are also many genetic conditions that are linked with CSF obstruction and may lead to hydrocephalus, including a chiari malformation, some of which are associated with neural tube defects like myelomeningocele or spina bifida. Other conditions that can block CSF flow include Dandy-walker syndrome (which is associated with an enlarged posterior fossa, that can be cystic and block CSF flow) and Klippel-feil syndrome (which is marked by fusion of at least two cervical vertebrae, and can also block CSF flow from the fourth ventricle).

Lindsey: One of the most common causes of hydrocephalus in children, especially those born prematurely, is intraventricular hemorrhage, or IVH. It is thought that the hemorrhage impairs the reabsorption of CSF through the arachnoid granulations, leading to hydrocephalus which may require surgical management.
Other causes of hydrocephalus include benign enlargement of the subarachnoid space, hydranencephaly, which causes absence of most of the hemispheres of the brain, and choroid plexus papillomas.

Claire: There are other things in the brain that can accumulate and cause increases in pressure too. Increased blood in the head may be caused by a hemorrhage or an arteriovenous malformation (also called an AVM).

Lindsey: Obviously, you can also have a mass-occupying lesion, in the form of a tumor, cyst, or abscess. These also will often result in hydrocephalus and have signs of increased intracranial pressure.

Claire: Other conditions that lead to increased intracranial pressure include idiopathic causes such as pseudotumor cerebri - also known as idiopathic intracranial hypertension or IIH, as well as infectious or inflammatory processes such as meningitis, metabolic abnormalities such as vitamin A imbalances, and toxin exposures.

And, although uncommon in newborns, increased bone may be caused by conditions that cause bone marrow expansion, such as thalassemia major. Increased bone may also be caused by primary bone disorders such as achondroplasia or osteogenesis imperfecta.

Objective 2: Important points on history

Lindsey: As with any assessment, you should perform a complete history. Here, we will highlight some important features to include in the history for a patient presenting with macrocephaly.

We will start with pregnancy and birth history:

For any pediatric presentation, it is very important to review the pregnancy. In the case of macrocephaly, we would be interested in whether the mom had any prenatal screening, and if those results were normal. Some of these screens test for neural tube defects, which can be related to macrocephaly.

Claire: It is also important to ask about any conditions or illnesses that occurred during pregnancy. Conditions like pre-eclampsia can cause asymmetric Intra-Uterine Growth Restriction, or an apparently large head compared to the baby's length and weight.

Lindsey: Asking about ultrasounds is key as well. Was anything flagged or monitored? And finally, we can ask about the method of delivery: was it a spontaneous vaginal delivery? Was a C - section for cephalopelvic disproportion required, which might indicate a large head at birth?

And it is always very important to ask; how is their growth? Have they been following their height and weight growth curves, and are they proportionate? (For example, are the height, weight, and head circumference within similar percentile ranges.) For this, it can be very helpful to have access to previous measurements and to plot them on a growth curve.

Claire: Next, it is important to ask about developmental history: How has their development been? Are there any concerns about delays in meeting milestones, or losing skills that they had previously learned? Kids with large heads may take longer to achieve head control, due to the increased muscle mass required to control a heavier head. Losing developed skills is called regression, and it is a very concerning finding. It is a red flag for an underlying pathological process that requires further workup. When performing a review of systems, make sure to ask about constitutional symptoms and signs of a possible brain mass such as morning headache, vomiting, or neurological deficits.

Lindsey: You should also review the child's past medical history. Do they have any other health issues that have been followed by a physician?

Claire: Another important aspect of the history is family history, starting with the family history of head size. Do other family members tend to have large heads? Do they need to find special hats or helmets because they can't fit into regular ones? This information, including measuring the parents' heads if there is any concern, can be very helpful.

Lindsey: It is also helpful to know if there is any personal or family history of neurologic disease, developmental delay, seizures, or genetic problems. Also ask about consanguinity as this can increase the chances of the child having any type of recessive genetic condition.

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Claire: For the history of presenting concern: our role here is to understand what brought the child to medical attention, and to ensure that we ask enough questions to rule out our red flags.

Lindsey: Evidently, red flags in this case would be a mass or obstruction causing raised ICP and hydrocephalus!

Claire: History suggestive of this includes: Vomiting (especially in the morning), headaches (if the child is old enough to complain of a headache), bulging fontanelle, sun-setting eyes, or scalp veins dilating when the child cries.

Lindsey: Is there any history of head trauma, or interventions involving the head? (such as surgery). Ask about focal neurological signs: Have they noticed if the child has stopped moving a part of their body, or had any changes in coordination or gait (if the child is walking).

Claire: Have the parents noticed any changes in the eyes? Is it hard to move them upward, or are they tilted downward? (This is the setting sun sign.) If the child is older, we can ask if they have double vision or trouble seeing. Raised intracranial pressure can cause a sixth nerve, or abducens nerve, palsy, such that the eye cannot completely abduct. (The reason CN VI is usually affected first is because it has the longest intracranial course of all the cranial nerves.). The parents may also have noticed a persistent head tilt if a VI nerve palsy is present, tilting the head helps the child to alleviate the resulting double vision.

Lindsey: Sometimes eye changes are hard to assess in an infant or young child, so ask the parent if their child looks at things, and is able to follow across a room (depending on what is appropriate for their developmental stage).

Last, a review of systems is important: we can ask about any infectious or meningitis symptoms, as well as a history of neurologic changes or neurologic events like seizures.

Claire: In our case of Lucy the 2 month old with a large head, it turns out that she has been completely healthy! Her immunizations are up to date and her development is normal. There were no concerns with the pregnancy and parents are not genetically related. There are no signs or symptoms or raised ICP. On family history, it turns out that her father has a very large head and needs hats custom-made!

Lindsey: Hmmm - I know what I am thinking….

Claire: Although her history is reassuring, don't form your full impression quite yet! In any child with macrocephaly, we need to perform a full physical examination.

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Objective 2 continued - Physical examination of macrocephaly

Claire: Again – as with any assessment, you should perform a complete physical exam.

Lindsey: Okay, but what should I make sure not to miss in a patient with macrocephaly?

Claire: Well, the most important thing to do is verify that it is true macrocephaly. Measure the occipito-frontal circumference and plot it on an appropriate growth curve. You can also observe for any dysmorphic features while doing this.

Lindsey: True, having an accurate head circumference measurement is crucial! And if we have previous measurements we can see if the child is tracking along their growth curve or if their head circumference is growing at a faster velocity and crossing percentiles.

Claire: Yes, and there are some facial features that can be seen in syndromes linked to macrocephaly. For example, children with lysosomal storage disorders may have what is described as coarse facial features - the most prominent of which is often a larger forehead.

Lindsey: And then in addition to measuring the head and looking for dysmorphic features, I suppose we would also want to feel the head. We can feel the sutures and fontanelle, as well as for any bony prominences.

Claire: Exactly! The fontanelle may be full or bulging in an infant with hydrocephalus, or increased cerebrospinal fluid buildup in the head. Also, the sutures may be “splayed” meaning that you will feel a gap between the bones.

Lindsey: It is also important to examine their eyes. You can assess their ability to gaze upward, as “sun setting” eyes are also associated with hydrocephalus. If you are able to, you can look at their pupillary responses and fundus - though you may eventually need help with this from your ophthalmology friends.

Claire: Another interesting way of looking for papilledema at the back of the eyes is using ocular point-of-care ultrasound! This is still in its research stages in children, but might be helpful for those kids who don’t cooperate with fundoscopy.

Lindsey: True! Another important aspect of the exam is to check the alignment of their eyes and the extra-ocular movements in all directions. Increased intracranial pressure from any source can cause a sixth nerve palsy. The 6th cranial nerve, or the abducens nerve, abducts the eye through the lateral rectus muscle. If it is weak, a child may not

be able to look to the affected side very well, or they might even have in-turning or cross-eyes at rest (called esotropia). Also assess for the position of the head and determine whether a head tilt is present.

Claire: As with any child, it is important to observe their function and development. While you are performing the history and the above examinations, you can see how they move around the room, how they interact with you, and if it is appropriate for their stage of development.

Lindsey: This will lead into your neurologic examination where you can take a closer look at their function and assess for any deficits.

Claire: Finally, you can look at the skin for any birthmarks or lesions that may be associated with neurocutaneous disorders. Lindsey - do you know what I am looking for on my skin exam?

Lindsey: Yes, you'd be looking for Cafe au lait spots for neurofibromatosis, children need at least 6 spots to fulfill that criteria along with at least one other feature, such as axillary or inguinal freckling. You can also look for any hypopigmented, or hypomelanotic, macules, which would raise suspicion for tuberous sclerosis.

Claire: Exactly. In addition to examining the skin, it is also important to do a full abdominal exam to assess for any other masses. Many children with metabolic disorders, specifically the lysosomal storage disorders which we referenced earlier, can be found to have hepatosplenomegaly.

Lindsey: And one more thing - but if they came with siblings or parents, we might also be able to measure their heads to see if big heads run in the family - as this might be more reassuring in the setting of an otherwise normal exam.

Claire: Exactly! In Lucy's case, her entire physical examination was normal. She was active, non-dysmorphic, and had a flat fontanelle. She had good tone and was able to move all her extremities against gravity. She smiled at us and tracked our faces in all directions without any limitations in eye movements. She held her head up really well on tummy time and her abdominal exam was normal without any masses or hepatosplenomegaly.

Turn's out dad's head is also fairly large when measured and plots around the 95th percentile for adult males!

Lindsey: Okay, so now that I know what to look for on physical examination, What are my options for investigations and management?

Objective 3: Investigations and management

Claire: Depending on your history, exam, and level of concern, there are many different investigations you can perform and management strategies you may take.

Lindsey: The most conservative would be to follow head circumference, health, and development at serial visits with measurements, to be reassured that everything is okay. This would be an option in Lucy's case, as everything else is otherwise reassuring!

Claire: Another potential avenue of investigations includes imaging.
For babies that you are concerned about hydrocephalus, and really any infant with a big head or rapidly rising head circumference, a head ultrasound is an easy and safe first step. For this examination, an ultrasound technician will use the fontanelle as a window to see into the baby's brain and assess for ventricular size as well as other abnormalities.

Lindsey: Keep in mind, this can only be done if the fontanelle is still open, and if there is a big enough window to view into the brain! Otherwise, we may need other forms of imaging like a CT or MRI.

If the head ultrasound is abnormal, it may warrant a referral to neurosurgery and potentially an MRI. There are certain procedures that they can do to alleviate pressure in the brain, depending on the root cause. Some of the most common of these entail the insertion of a ventriculoperitoneal shunt, that drains CSF into the abdominal cavity, or putting a hole through the floor of the third ventricle to allow CSF to flow: an endoscopic third ventriculostomy (or ETV).

Claire: If the imaging is normal but the head is still large, the investigations you pursue would likely depend on whether there was anything else that you saw on examination.

Did the child have developmental delay? Did you notice dysmorphism or any specific skin findings? In these cases, you may pursue additional genetic or metabolic investigations, or a developmental assessment to consider autism spectrum disorder and identify whether intervention or supports are needed.

Lindsey: You may ask ophthalmology to evaluate the child or you are concerned about papilledema or limitations or the extraocular eye movements. You may also consider referral to a tertiary pediatric centre where an LP can be performed, if deemed safe to do so, to test CSF and measure opening pressure.

Claire: If the child is dysmorphic or has other concerning physical features on examination, you may pursue an echocardiogram, abdominal ultrasound, metabolic

evaluation, genetic studies or even an EEG if seizures or encephalopathy are on the differential.

In addition, if the child has developmental delay, a referral to a general pediatrician or developmental colleagues may help ensure that they have appropriate services and supports to reach their potential!

Lindsey: And finally, if the child has a large head but otherwise normal investigations and physical examination, you may choose to monitor the child with serial growth parameters, like we mentioned previously.

Claire: Exactly! Let's recap Lucy's case. Lucy is a 2-month-old girl who was referred for potential macrocephaly. Her head circumference was at the 75th percentile at birth, but is now at the 97th percentile. We saw this patient multiple times to get multiple measurements. Turns out, her head circumference was trending along the 97th percentile with an appropriate growth velocity! Also, when we plotted her length and weight, they were also both tracking along the 95th-97th percentiles. So, our patient's growth parameters are proportionate, and she doesn't have any other concerning features. No further workup is needed! On further history we also found out that her dad has to special-order custom hats because of his large head size - it runs in the family!

Lindsey: That concludes part 3 of our series, covering an approach to macrocephaly. Let's review what we discussed:

Review

- Macrocephaly is defined as a head that is bigger than the 97th percentile.
- There are many causes of macrocephaly, and the easiest way to approach this is to run through the multiple things that you find inside the head: the skull, the brain, cerebrospinal fluid, blood, and then of course the possibility of other masses.
- Having an idea of the growth trajectory is important to see if a child's head has always been on the large side or if it is progressively getting larger.
- One of the most important things to rule out in cases of macrocephaly is a space-occupying mass, inside the head.
- Hydrocephalus is when cerebrospinal fluid accumulates in the closed space of the skull. If a baby's sutures and fontanelle have not fused yet, it can cause the skull to enlarge and the fontanelle to "bulge".
- It may also cause the eyes to look down, a term called "sun setting".
- Other symptoms of raised intracranial pressure are morning vomiting and headache.
- A sign of elevated ICP is papilledema on fundoscopy! (or swelling of the optic disc!)

- Raised ICP can also cause a 6th cranial nerve, or abducens nerve palsy.
- Other causes of macrocephaly are a large brain (which can sometimes be seen in children with autism), or enlargement of the bony areas of the skull, which can be secondary to extramedullary hematopoiesis in things like thalassemia.
- If there are concerns about macrocephaly, head imaging like an ultrasound or MRI can be useful, as well as referrals to other specialists, like neurosurgery or ophthalmology.

Amazing, thanks! Stay tuned for our last and final podcast of the series, covering microcephaly.

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