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# Approach to Abnormalities in Head Shape and Size Part 4: Microcephaly

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 the fourth and final part of our series on head shape and size. My name is Lindsey Logan and I am a pediatric neurology resident in Toronto.

**Claire:** And I am Claire McNiven, a pediatrics resident at the University of Alberta. 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 the first three podcasts, we reviewed: head growth and skull anatomy, an approach to abnormal head shape, and an approach to abnormally large, or macrocephalic, head size.

**Claire:** If you need a refresher, feel free to rewind to parts 1-3 where we cover all of that in detail! Otherwise, continue on and we will cover our last objective - Microcephaly.

**Lindsey:** "Micro" means "small" in Latin, so microcephaly is the opposite of macrocephaly – now we're talking about a small head!

Our Objectives for the final edition of our podcast series are

1. Define microcephaly and Differentiate primary and secondary microcephaly
3. Determine the differential diagnosis for a child presenting with microcephaly
4. Review key points on history and physical exam which will help determine your differential diagnosis
5. Review an approach to investigations and management of children presenting with microcephaly

**Claire:** Microcephaly is defined as head circumference more than 2 standard deviations below the mean for age and sex of the patient. 2 standard deviations below the mean is the 3rd percentile.

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**Lindsey:** Here are two separate cases to get you thinking:

*Case #1*
Jasmine visits the community pediatrics clinic where you are on placement. She is a 2 year old girl with a history of gross motor delays: she sat at 9 months, and is not yet walking. Her parents bring her in because Jasmine is no longer making eye contact and no longer helps to feed herself at mealtimes. You measure her head circumference and note that it is below the 3rd percentile.

*Case #2*
You are a med student on your community pediatric hospital rotation when you are called to examine a newborn baby boy born to a healthy mother for concerns of small head size. The birth was uncomplicated however on further history you discover that mom is originally from Brazil and that the baby's father travelled to Brazil on numerous occasions during the pregnancy. When you first see the baby, you notice that he has an alarmingly small head with a subtle indentation of the forehead.

**Claire:** Keep those cases in mind as we work through our approach, starting with the differential diagnosis of microcephaly.

## Objective 1: Definition of microcephaly

**Lindsey:** Again, changes in size of anything in the head can lead to microcephaly, and it is important to keep this in mind when thinking of our differential. The biggest thing inside our head, which our skull is protecting, is our brain! As one of my mentors has said "small head means small brain!". If the brain doesn't grow at the expected rate, then the skull does not have to expand or grow with it.

**Claire:** Conditions that cause microcephaly can be broken into two categories: Primary and Secondary.

**Lindsey:** However, it is important to remember that these classifications are sometimes more academic, and it may be difficult to neatly classify all cases.

**Claire:** Most of the time, primary microcephaly refers to conditions where the brain never formed properly because of genetic or chromosomal abnormalities. In primary microcephaly, the brain and surrounding tissue forming the head were always meant to be small.

**Lindsey:** And Secondary microcephaly indicates that the brain did not form properly because of an acquired problem. In secondary microcephaly, the brain and head had the potential to be normal (and at one point may have been growing normally!) and then something happened to cause the growth to slow, resulting in a microcephaly. Some

people regard secondary microcephaly as only occurring after birth, however here we will discuss it as any insult that caused microcephaly, either in utero or after birth.

## Objective 2: Differential diagnosis of microcephaly

**Claire:** Disorders falling into the category of primary microcephaly include chromosomal or genetic defects, of which there are many! These children are often short, may have dysmorphic features, and often also have developmental delay, as our first case does, which may lead to intellectual disability later in life.

Common genetic and chromosomal associations with microcephaly include trisomies (13, 18, 21), Angelman syndrome, and other genetic disorders which may be autosomal dominant, recessive, or X-linked disorders relating to cell division and proliferation of the cells of the brain.

**Lindsey:** Other disorders falling into the category of primary microcephaly include disorders of neurulation, some of which may have a genetic origin - beware that some of these may also be from secondary causes as well! In any case, disorders of neurulation basically means disorders of the formation and closure of the neural structures. The most severe of these is anencephaly, which means that a child is born without parts of his or her brain and skull. Rates of anencephaly are declining due to improved prenatal care and ultrasound screening.

Another spectrum of disorders of brain growth and proliferation are the malformations of cortical development. These include holoprosencephaly, where the brain, and sometimes other structures on the face like the eyes, fail to divide. These children only have a single brain hemisphere, instead of two, and therefore have smaller heads.

**Claire:** A last disorder that falls under the malformations of cortical development is lissencephaly. “Lisse” means smooth, and lissencephelaly is a condition where the brain does not properly form folds (also known as gyri) and grooves (sulci) resulting in a smooth surface and a smaller brain and head.

**Lindsey:** The gist of primary microcephaly it is that “primary” refers to something pre-determined very early in development such that the skull never had potential to be a normal size. Secondary microcephaly is where the skull had potential, and may have been developing normally, but something was acquired which slowed its growth.

**Claire:** Disorders falling into the category of secondary microcephaly include intrauterine disorders, such as infections, substance exposures, or perinatal brain injuries. These can all cause microcephaly by slowing the growth of the brain or head. A few common congenital infections that can result in microcephaly include toxoplasmosis, cytomegalovirus, and zika virus.

Congenital toxoplasmosis occurs when a pregnant mother is infected by Toxoplasma gondii, often from handling meats, raw or unwashed vegetables, from gardening or changing cat litter.

**Lindsey:** Pregnant women are advised not to change cat litter for this very reason!!

In neonates, congenital toxoplasmosis often affects the nervous system and can also affect the eye, causing something called chorioretinitis, which means inflammation and infection of the posterior, vascular region of the eye.

**Claire:** Another one of the most common congenital infections that causes microcephaly is cytomegalovirus, or CMV. Congenital CMV infection affects 0.5-1% of live births in North America and Europe, and up to 6% in developing countries. It can occur when a mother is previously infected or infected during pregnancy with the cytomegalovirus. It is most commonly transmitted through bodily fluids such as saliva, urine, sexual secretions and breast milk.

**Lindsey:** Oh wow, interesting! And you also mentioned Zika virus, which I remember was a big deal, especially when the Olympics were in Brazil in 2016.

**Claire:** Yes, Zika virus has become more prevalent in certain areas of the world, though rates have thankfully gone down in the past couple of years. Zika virus is spread by the Aedes aegypti mosquito, and can also be found in blood and bodily fluids. Expectant mothers can be infected by travel to endemic areas or by sexual contact with a man who has Zika virus. There may be minimal symptoms, however many mothers of children later diagnosed with Zika may recall a pruritic maculopapular rash.

**Lindsey:** Other causes of secondary microcephaly include intrauterine toxins and drugs - commonly mentioned drugs are thalidomide and valproic acid. Secondary microcephaly can also be caused by brain injuries, such as hypoxic ischemic encephalopathy (HIE), stroke, meningitis, and encephalitis. Finally, systemic diseases like cardiopulmonary disease, renal disease, and malnutrition may also contribute to secondary microcephaly.

Another category that is difficult to classify that may present with microcephaly is metabolic disorders. Although these are technically due to underlying genetic problems that cause defects in the metabolism, these children usually appear normal at birth and in early life because they had the benefit of the placenta and their mother's metabolism in utero. They may present with progressive problems as they grow, which could be worsened by specific stresses or insults.

**Claire:** All that to say - there are many things to keep in mind on the differential diagnosis for microcephaly, and a very important factor in determining further investigations and treatment is our history.

## Objective 3: History and physical examination

**Lindsey:** As with all of the disorders of head shape and size, it is important to take a full and complete history. Here, we will focus on pertinent areas only:

**Claire:** If we go in order of timing, we can start with pregnancy. Lindsey, what kind of things would you want to ask mom about her pregnancy?

**Lindsey:** I would want to know about her prenatal care, if she was followed. If the pregnancy was planned, or unplanned, and if she had any exposure to drugs or toxins. Has she had ultrasounds? Were there any concerns with her measurements? Any abnormalities in her blood tests? Gestational hypertension is also an important thing to ask about, because preeclampsia can cause IUGR, or intrauterine growth restriction, which if severe can also affect the head size.

Last, I would want to ask about exposure to infectious agents:

- Any travel history for her, her partner, or other family members?
- Does she have other children? Do they go to daycare?
- Does she have pets? (remember, cat litter can expose pregnant women to toxoplasmosis!)
- Does she recall being sick at all at any point during the pregnancy? Specifically, any fevers, rashes, or other illnesses. You can also ask about sick contacts during her pregnancy.

**Claire:** And pregnancy history always eventually leads into birth history… what is important to ask here?

**Lindsey:** We always ask how the baby was born and especially at what gestational age (remember, we are using corrected GA up until 2 years of age!).
We can also ask about any trauma during birth and if the baby required any resuscitation or NICU stay. Did they have any other medical problems like jaundice, or anything that was detected on their metabolic screen?

**Claire:** Then we can ask how the child has been up until this time, which includes medical and surgical history, as well as a thorough growth/nutrition and developmental history to understand if the child is delayed or developmentally appropriate.

**Lindsey:** As part of a focused review of systems, you can always ask about neuro-specific symptoms as well, such as seizures or stereotyped movements.

**Claire:** I would also ask if the child has had hearing and/or vision screening and if there have been any concerns.

**Lindsey:** Last, asking about a Family history of developmental delay, neurological, genetic, or metabolic problems, and seizures will also be important. Family history should include 3 generations in cases of recessive disorder.

**Claire:** For recessive disorders, again, it is very important to ask about consanguinity as this increases the chance of a genetic recessive disorder. You can also ask about ethnicity.

**Lindsey:** And don't forget to ask about family history of head sizes!

**Claire:** So, what kind of information can we get from our cases on history?

**Lindsey:** If you remember, Case #1 is Jasmine, the 2 year old with developmental delays. Mom had an uneventful pregnancy and she was born at term. She was growing well for the first few months of life, smiling and interacting, and was rolling front-to-back at 5 months. She sat unsupported at 9 months of age but has not yet walked independently. She can sometimes pull to stand with help but parents remark that she is "not very stable".
More recently, she has stopped making eye contact, and also stopped performing fine motor tasks like assisting with feeding herself, and she is no longer colouring with markers. She previously had a repertoire of approximately 5-10 words which she no longer uses. The parents state that she has been otherwise well, with no other medical concerns. They do not believe that she has had seizures but they have observed abnormal breathing patterns, after which she has fainted a couple of times.

There is no history of trauma or previous infection. She has no siblings and family history is otherwise unremarkable.

**Claire:** Wow, interesting. The developmental regression of language and fine motor skills is certainly a red flag. Because she is a female, I wonder about Rett syndrome and other variants of Rett syndrome, so I will keep that in the back of my mind while we move on to physical exam.

**Lindsey:** Good thinking! Rett syndrome is a genetic disorder that leads to neurologic impairment and occurs almost exclusively in girls. It can be associated with regression, abnormal breathing, as well as microcephaly, so it is a good thought! There are also other genetic disorders that can present similarly to Rett syndrome but have different causal mutations.
Can you tell us about case #2?

**Claire:** Sure! Case number 2 was the newborn with microcephaly and Brazilian parents, who we met just after birth given concerns for microcephaly. There is not much on history here since the baby was just born, however we do establish that mom remembers having an itchy rash early in her pregnancy, a few weeks after the father returned from Brazil.

**Lindsey:** Hmm, now I am definitely thinking about congenital infections that predispose to microcephaly, like CMV or ZIka. Brazil is an endemic area for Zika virus so I will keep it in the back of my mind as well!

**Claire:** Yes, it is good to begin establishing a differential during the history, but don't forget, you are missing another very important piece of information to guide your final impression.

**Lindsey:** Exactly - let's move on to physical examination!

## Objective 3 Continued: Physical examination

**Claire:** I am going to sound like a broken record again, but it is important to do a full physical examination! Here, instead of reviewing steps of a full physical examination, we will discuss the pertinent aspects of a physical examination in a child with microcephaly.

**Lindsey:** First up: Observation. You can observe the child to see if they have any dysmorphic features, and if they are acting in a developmentally appropriate manner. Is their resting tone normal? Do they move around like you would expect, and interact appropriately? Do they show any stereotyped movements or neurological abnormalities?

Next - confirm the head circumference! Measure and plot the head circumference, alongside the other growth parameters like height and weight. Remember to correct it if the child was premature!

**Claire:** After this, it is important to fully examine the child. Check the skin for any rashes, specifically looking out for petechiae (which may be seen in congenital CMV infection) and jaundice.
When examining the back, look at the base of the spine for any sacral dimpling.
As part of the general exam, also look out for hepatosplenomegaly or any abdominal masses. Hepatosplenomegaly could be indicative of a congenital infection such as CMV.

**Lindsey:** As part of the neurological examination, assess the eyes for any signs of redness, abnormal pupillary response, defects in the red reflex or abnormalities on fundoscopy - if you are able to perform this!

Remember, in a child with microcephaly you may find chorioretinitis, which is associated with congenital infections - or cataracts which is associated with metabolic diseases. If you can't get a good look at the eyes, it is always a good idea to ask ophthalmology if they would be able to assess.

**Claire:** Then perform the rest of the neurologic examination, including primitive reflexes if applicable, and vision and hearing response. On motor examination, assess tone and deep tendon reflexes as well.

**Lindsey:** Last, you can also measure the parents' heads - we can use something called the weaver curve in a child without syndromic features, to determine if the child's head circumference is appropriate given their parental head circumferences.

**Claire:** What did we find for our cases on examination:

**Lindsey:** Case #1, Jasmine, our 2 year old female with microcephaly and delays, showed obvious developmental abnormalities on examination. She did not make eye contact and barely engaged with us or her parents throughout the assessment. She did not use words and displayed some stereotypies including waving her hands. She also displayed some odd breathing patterns. On observation, she appeared to have some dysmorphic facial features however these were subtle and very difficult to ascertain. Her tone was slightly reduced but she otherwise had a normal neurologic and general examination, with normal pupillary responses. Her head circumference, as mentioned previously, was below the 3rd percentile.

**Claire:** Our neonate in case #2's examination is notable for obvious microcephaly, with a partially collapsed superior skull. He also has hypertonia and some congenital contractures (also known as arthrogryposis) at the ankles.
His abdominal and skin examinations are normal. It was difficult to get a look at his eyes so this was deferred for evaluation by an eye specialist.

**Lindsey:** Hmmm… thats very interesting. For Jasmine's case, I am also still wondering about a genetic or chromosomal problem. For case #2, given the Brazilian link and the obvious flattening of the head, I am thinking of congenital infection including Zika virus!

**Claire:** Great, now let's talk about possible investigations and management.

## Objective 4: Investigations and management

**Claire:** Make sure you have access to heel prick/ newborn screening to confirm that they are normal. The mother may even be able to provide you permission to access her chart and look into the ultrasound scans that detail head circumference or bi-parietal diameter (or BPD).

**Lindsey:** In some cases, if there is concern for congenital infection or any ocular abnormalities, an ophthalmology consultation is useful. They can look for any signs of chorioretinitis or other eye problems.

**Claire:** In terms of imaging, we have a few options:

First off, head ultrasound is a great imaging modality that is very accessible and provides a window through the fontanelle. With this test, you would be looking for calcifications and other signs of congenital infection.

**Lindsey:** Another option, especially if there are seizures, an abnormal neurologic examination, or concerns for other intracranial abnormalities, is MRI. You can also add MRS (which stands for MR Spectroscopy) which looks at the chemical composition of specific regions (called voxels) of the MRI. Certain chemicals give off different signals, and it can help if you are worried about a metabolic problem.

CT is often a less preferred for evaluation of microcephaly.
What about lab work?

**Claire:** That's a good question! It definitely depends on what you are worried about:
If you think the child may have a metabolic problem, the following are the typical metabolic screening labs:

- VBG, lactate
- Ammonia
- Acylcarnitine and total carnitines
- Plasma amino acids
- Urine organic acids

**Lindsey:** If you think the etiology could be genetic or chromosomal, it may be worth considering a karyotype, microarray, targeted genetic testing, or a referral for WES - or whole exome sequencing.
If there is suspicion for seizures, an EEG is important to procure.

**Claire:** If there is suspicion for congenital infection: infection specific screening is usually important for confirmation. This generally includes antibody testing (serologies), and confirmatory tests of infection (PCR) if possible.
The gold standard test for congenital CMV infection is CMV urine PCR prior to 3 weeks, or 21 days of life. If this is confirmed, follow-up testing such as CBC, bilirubin, and liver enzymes is indicated.
For an infant with features suggestive of congenital Zika infection, the CPS statement suggests obtaining serology (both in blood and urine) and a Zika PCR for the mother and the child, as well as a head Ultrasound and brain MRI on a non-urgent basis.

**Lindsey:** In addition to any infection specific testing, for pretty much all suspected congenital (or TORCH) infections, a Head ultrasound, hearing evaluation and ophthalmological evaluation are important.

**Claire:** So, going back to our two cases:

Our first case, Jasmine, is our 2yo with developmental delay and recent regression, microcephaly, motor stereotypies such as hand waving, abnormal social behaviour and low tone.

**Lindsey:** Her story evokes a strong suspicion for primary microcephaly of a genetic or chromosomal etiology. She does have some tone abnormalities but no other red flags such as seizures or focal neurological problems, but given her regression, neuroimaging in the form of MRI (plus MRS) will likely be important. Also, if she does have any seizures, especially if they are unprovoked, I would get an EEG and MRI right away.

Given her slightly dysmorphic facial appearance and her regression, we can likely start with some screening blood tests to ensure that there are no metabolic concerns (remember, she did have some odd breathing patterns), like a CBC, VBG, lactate, liver enzymes, ammonia, free and total carnitines, plasma amino acids, and urine organic acids. In terms of other tests to confirm an etiology, a microarray or even specific genetic testing for Rett Syndrome, given that it is high on our differential, might be the most appropriate place to start. The genetic testing can be initiated by the pediatrician or it can be referred on to a developmental pediatrician, pediatric neurologist, or geneticist for further management.

**Claire:** Regardless, while we are arranging investigations, she will likely need a full developmental assessment to allow her appropriate supports and services as she grows.

**Lindsey:** Exactly! Claire, can you tell us about our second case?

**Claire:** Yes, this was the term newborn baby boy for whom we were called for microcephaly. He was otherwise stable but had hypertonia with contractures of the ankles. Given the paternal travel history to Brazil and his physical appearance, we strongly suspected congenital Zika Virus. As per the CPS statement we decided to arrange for Zika testing in the baby and his mother, and also arranged a head ultrasound, ophthalmology assessment, and hearing screen.

**Lindsey:** Sounds good! That brings us to the end of our podcast on microcephaly. Let's recap what we reviewed:

## Review

- Causes of microcephaly are often split up into primary and secondary.
- Primary microcephaly usually pertains to something genetic, such that the brain, and therefore the head, were never destined to be normal size.
- Secondary microcephaly refers to microcephaly where the brain and head were forming normally and then an insult, or infection, occurred, causing the growth to slow down.

- Again, with microcephaly, it is important to measure the child's head, compare it to the size of the rest of their body, and plot the growth over time.
- Also, pay attention to other factors such as dysmorphism or developmental delay.
- Imaging microcephaly can also be done by a US, CT, or MRI depending on what is most appropriate for the child.
- Referrals may also be required to ophthalmology to evaluate the eyes, development for an assessment and identification of appropriate developmental services, or neurology, especially if there are suspected seizures.

And that's it for our pedscases podcasts on head shape and size.

Thanks everyone for listening, we had a great time reviewing our approach to head shape and size with you all!

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