Theories on What Causes Chiari

Open Access: A new hypothesis for the pathophysiology of symptomatic adult Chiari malformation Type I

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Background
Current theories about Chiari can't explain why many people have tonsillar herniations greater than 5mm but don't have symptoms, or why the amount of herniation is not strongly related to symptom severity. This is a new theory that is built on a substantial number of existing publications, plus preliminary evidence developed at the Conquer Chiari Research Center (CCRC).

Hypothesis
The new theory has several parts:

1) In addition to tonsillar herniation (which is more common than originally believed), CMI patients have structural abnormalities of the atlanto-occipital (skull-spine) and atlanto-axial (top two spine vertebrae) joints which leads to subtle, but chronic instability

2) This instability causes the sub-occipital muscles in the neck to be overworked as they constantly engage in order to provide support

3) This leads to mechanical failure of the Myodural Bridge Complex (MDBC). The MDBC is a group of connective tissues that link the sub-occipital muscles to the dura covering the upper spine.

4) The failure of the MDBC causes the dura to become stiff and less compliant.

5) The combination of tonsillar herniation and reduced compliance creates an abnormal pressure environment where during the normal cardiac cycle, and especially during Valsalva or exertion, there is a pressure spike in the brain compared to the spine.

6) This leads to strain on the cerebellum, brainstem, and cervical spinal cord causing many of the common Chiari symptoms.

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Small Skull or Big Brain?

The first modern theory of Chiari proposed that Chiari patients' skulls are too small, specifically in the posterior fossa region where the cerebellum is housed. Basically, as the brain grows normally there is not enough room and it ends up growing some outside of the skull. Indeed some early morphometrics research found that the posterior fossa of Chiari patients tends to be small.

However, over time other research found this is not always the case. In fact, a 2015 study (Roller) found that age, sex and BMI all play a role in posterior fossa size and that when these are controlled for there is actually no real difference between the posterior fossa volume of adult Chiari patients and healthy controls.

This confusion has led some in the Chiari research and medical community to essentially group patients into what they call Classic Chiari with what appear to be small posterior fossas and other types of Chiari patients with normal sized posterior fossas. The scientific basis for this separation is not yet clear as there is no evidence that these groups differ in any meaningful way in terms of symptoms and outcomes.

While the evidence is very strong that Chiari patients have skull base abnormalities, and the primary treatment for Chiari is in part focused on essentially creating a larger posterior fossa, it does not currently support the small posterior fossa theory in its entirety.

Push, Pull or Both?

In contrast to the posterior fossa theory, another possibility for tonsillar herniation is that the tonsils are being pulled out of their normal position due to a pressure imbalance between the spinal fluid (CSF) in the skull and the spine. Basically, if there is enough crowding around the tonsils the CSF can't flow properly between the skull and spine areas and this can lead to a pressure imbalance. So if the pressure is lower below the tonsils maybe they are being pulled down, or stretched.

There is some evidence to support this. Specifically, the morphometrics studies from the CCRC found the lower half of the cerebellum is elongated in Chiari patients and the DENSE studies found high levels of strain on the lower parts of the cerebellar tonsils. However it is not currently known what the pressure environment would have to be to actually pull the brain tissue down, and of course this doesn't address why some people have large herniations with no symptoms.

So to summarize Chiari patients have tonsillar herniation; skull base abnormalities; disrupted CSF flow; and abnormal motion of the brainstem and cerebellum; however determining the "cause" of these things is proving to be difficult. The tonsillar herniation could be due to the cerebellum being pushed out from too small of a space, being pulled out by a pressure imbalance, or some combination of both.

Role of Body Mass Index (BMI)

There have been a couple of studies that have found that Chiari patients, both adult and pediatric, tend to have higher BMIs than average. This has led some to speculate that BMI can play a role in causing Chiari. While this may be true in terms of symptoms, a study from Michigan (Maher) showed pretty convincingly that BMI does not influence tonsillar position. Specifically, the study drew from a pool of 2400 MRIs which was created by randomly selecting 300 subjects from each of 8 age groups ranging from newborn to 80. From this group, 1300 had BMI information from within 1 year of the MRI scan. Based on this data they found no correlation between BMI and tonsillar position for any age group. It is important to note that the study group even included 46 people with tonsillar position greater than 5mm, but even for them there was no correlation with BMI.

Evolutionary

One of the more interesting theories to emerge over the last decade posits that evolutionary issues may play a role in Chiari. In a 2013 paper, Fernandes highlights that the skull base has seen significant change over the course of human evolution, and that the skull base is used by anthropologists to classify hominids. He further points out that Neanderthals tended to have flatter skull bases as is seen with many Chiari patients. While the paper is purely speculative, it also coincides with a growing recognition in the scientific community at large that there was more interchange of genes between Homo sapiens and Neanderthals than initially believed. In fact, recent genetic studies have shown that most people have about 2.5% Neanderthal genes with some being much higher. Currently there is no patient focused data to either support or disprove this theory, but it would be interesting to test Chiari patients for their percentage of Neanderthal DNA.

Instability

A recent theory proposed out of India (Goel) suggests that the root issue for Chiari patients is actually cervical instability, even when there is no evidence of this instability on imaging. Goel has published results of performing spinal stabilization surgery for Chiari rather than traditional decompression surgery. However, the number of patients treated this way is so far quite limited and others in the neurosurgical community have criticized this approach. To date, there is no

indication this theory and approach is being accepted in the US, but internationally there are now several publications on this topic.

Tight Filum Terminale (Recognized Cause of Tethered Cord Syndrome)

Another controversial theory that arose awhile back is from a Spanish neurosurgeon, Dr. Royo-Salvador, who hypothesized that a tight filum terminale leads to Chiari by pulling down on the spinal cord. The filum terminale is a fibrous, thread-like extension of the bottom of the spine. The filum is normally elastic, but sometimes it becomes fatty and can be abnormally tight. When this occurs, it essentially pulls down on the spinal cord.

A tight filum is a recognized cause of tethered cord syndrome and can cause bladder and bowel problems and leg weakness, but Royo-Salvador proposed that the spinal traction caused by a tight filum also can lead to Chiari, syringomyelia, and scoliosis. He published a report indicating that a simple surgery to cut the tight filum improved Chiari symptoms in a number of patients.

Unfortunately, his report did not indicate how he selected patients for this procedure and the outcomes were not well defined.

Beyond Royo-Salvador's publication the evidence regarding a tight filum as a possible cause of Chiari is mixed. One research group did find that children with lipomeningoceles – fatty tissue that protrudes out of the spinal cord – had an unusually high rate of Chiari malformation. One possibility for this was that the defects were tethering the spinal cord and causing downward traction. However, this same group subsequently performed a study using cadavers where weights were attached to the bottom of the spinal cord to simulate a tight filum or tethering at the bottom of the cord. They found that the mechanical force induced by the weights was dispersed very quickly moving up the cord and that they did not affect the position of the cerebellar tonsils at all. However Ellenbogen published the case of a 3 year girl who developed Chiari as a result of a fatty, tight filum. The report included MRI images that were taken both before and after Chiari developed.

A number of years ago Conquer Chiari funded a well-known neurosurgeon to evaluate tethered cord surgery as related to Chiari. However, after only a couple of procedures the surgeon stopped the project because he felt there was not sufficient evidence to support treating patients that way and therefore it would be unethical to continue.

It is important to note that some patients have both Chiari and clear evidence of tethered cord, but there is a lot of skepticism among the Chiari community about tethered cord actually causing Chiari and even more about sectioning the filum terminale to treat Chiari.

Genetics

Some diseases, such as Huntington's, have a straightforward genetic component which can lead to the development of a genetic test. Chiari is NOT such a disease. Rather the genetic component of Chiari appears to be complex and to date a 'Chiari gene' has proven elusive. In fact, it may be the case that the genetic component is different for different types of patients, likely includes several genes, and it is not even clear what those genes control.

Environmental Factors

Chiari seems to be a complex medical condition, so it would not be surprising if it involves both genetic and environmental factors. Unfortunately, there has been even less research on environmental factors than there has been on the genetics of Chiari. However, two interesting studies indicate that pre-natal exposure to different substances can lead to Chiari type anatomy.

First, a 1984 study found that a single dose Vitamin A given on the eighth day of gestation in pregnant hamsters led to Chiari malformations in the hamster fetuses. The study also found that both the percentage of fetuses with the malformation and the severity of the malformations increased as the Vitamin A dosage increased. While the Vitamin A doses were quite large, the study does demonstrate pretty clearly that the fetal environment is capable of influencing Chiari related anatomy. However for reasons that are not clear, there has been follow-up to this line of research.

The second study involved pregnant women taking Selective Serotonin Reuptake Inhibitors (SSRIs), which are a group of antidepressants. Specifically the 2014 study looked at three groups of children: 33 children whose mothers were diagnosed with depression and took SSRIs during pregnancy; 30 children whose mothers were diagnosed with depression but did NOT take SSRIs during pregnancy; and 60 children whose mothers were not depressed and did not take SSRIs. MRIs were available for the children at the age of 1 or 2 years as part of a different study involving SSRI use. The researchers found, by accident, that 18% of the children in the SSRI group showed Chiari malformation on MRI compared to the expected 2% of the non-depressed, no medication group. In addition, the rate of Chiari was not different between the depressed group and the control group.

Finally, duration of SSRI exposure and SSRI exposure at conception were also linked to the presence of Chiari. To be clear, these results refer only to tonsillar herniation, and not symptoms. At the time the study was published none of the children had Chiari like symptoms, but it does raise the question of whether they will develop symptoms later in life. It also clearly shows that environmental factors during pregnancy can lead to Chiari type anatomy. There is also evidence (discussed more later in this chapter and in the book) that environmental factors such as trauma and physical labor can play a role in the development of symptoms. Therefore, environmental factors may play a role in both the development of Chiari anatomy and the onset of symptoms.

Acquired Chiari

As opposed to the above theories, acquired Chiari is fairly straightforward and well understood. Basically, any mass inside the skull, such as a tumor or cyst in the posterior fossa region, can cause crowding and force (herniate) the cerebellar tonsils out of the skull. In addition, Chiari can also result from problems with the CSF system, such as hydrocephalus, which result in the tonsil being forced out due to pressure.

Chiari can also be acquired from CSF leaks. A tear in the dura of the spine, say due to some type of physical trauma, can lead to a drop in CSF pressure below the brain and essentially pull the brain tissue down into the spine.

Trauma

While the role of trauma in dural tears and CSF leaks is straightforward, there are also many anecdotal reports of people developing symptoms and being diagnosed with Chiari after traumas such as car accidents. In fact, Milhorat found that 24% of symptomatic patients reported some type of trauma as a precipitating event in developing symptoms. The Chiari1000 found that 21% of patients reported that symptoms were triggered by a specific event, with pregnancy, car accidents, and falls being the most common. However, the question is whether trauma only plays a role in sparking symptoms, or whether it can actually lead to the cerebellar tonsils herniating. In other words, do some people already have a Chiari-like anatomy and an accident, for reasons that aren't clear, triggers their symptoms, or can trauma actually cause an anatomical change?

Several people have reported to Conquer Chiari that they have MRI evidence that the whiplash from car accidents actually caused their cerebellar tonsils to herniate. Unfortunately, such cases have not been published in the medical literature and subjected to the peer review process, so many doctors remain cautious in saying that trauma can actually cause acquired Chiari. Complicating the situation is the fact that many of these cases have legal ramifications due to lawsuits over car accidents and workers compensation claims.

Myelomeningocele

The discussions above refer to Chiari I. Since Chiari II is almost always associated with spina bifida, it is believed to be a result of the spinal defect. In spina bifida, the spinal cord does not close properly during development.

One theory on Chiari II is that this opening alters the CSF pressure, which in turn can cause parts of the brain to descend out of the skull.

A second consideration is the idea that CSF pressure in the skull is necessary for normal skull growth. In other words, during development CSF pressure builds to a certain level in the skull, which essentially pushes out the skull plates and guides normal skull development. When the spinal cord does not close, the proper CSF pressure is not maintained resulting in lack of skull growth and herniation of the brain. Interestingly, while this theory of skull growth was very popular a number of years ago, some developmental biologists now feel the theory is outdated.

Given the amount of research attention focused on spina bifida, it is surprising that the link to Chiari has not been explored in more depth, but there are actually very few publications on this subject. Another subject which is not written about or discussed as much as it should be is whether Chiari I and Chiari II are related or are they distinct clinical entities. In other words, are Chiari I and Chiari II due to the same underlying cause; do they lie on the same spectrum with Chiari II being more severe?

The prevailing wisdom is probably that they are two separate conditions, however as mentioned earlier in this chapter there are people with features of both Chiari I and Chiari II. In addition, if proper CSF pressure is required for normal skull growth, and Chiari I patients tend to have small posterior fossas, one has to wonder if a temporary drop in CSF pressure – such as due to an opening which then heals on its own – may be the problem.