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Cleft Lip and Palate Repair: Bridging the Gap between Genetics and Oral Health

An Individual Case Study

2013

BY

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Biology

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INTRODUCTION TO CL/P

The human body is so intricately designed that each organ and orifice is closely related and precisely interwoven. The human oral cavity, or mouth, is an example. Not only does the mouth provide the means for nutrient uptake, but it is also a prime environment to host a number of different bacteria that aid in digestion. One of the factors that makes the mouth a key environment for bacterial growth is the abundance of teeth that individual niches for many bacteria. The adult human mouth contains up to thirty-two permanent teeth. Each tooth is covered with ridges and crests which provide vast amounts of surface area for bacterial growth. When adults eat, they do not swallow all of their food, leaving behind residues and particles that serve to nourish the bacteria in the mouth. Thus, the cycle of life continues: humans taking in nourishment to sustain their personal homeostasis, and which supports oral bacterial growth. However, sadly this is not the case for all people. The condition known as Cleft Lip and Palate Syndrome is a condition that makes life rather difficult for those who have it. In part, this is because of an increase in bacterial infections, due to the inability to effectively clean the mouth (De Moura, *et. al.*, 2013). However, because of modern medical procedures, the incidence of serious health issues in Cleft Lip and Palate patients is beginning to ebb.

Cleft Lip and Palate Syndrome (CL/P) is a condition that occurs in vitro, during fetal development. During the final stages of development, certain groups of connective tissues in the fetus's maxillofacial and nasal region fail to connect. When this occurs, there can be severe consequences. The most severe deformity is CL/P. CL/P causes the tissues of the hard palate, part of the soft palate, and also regions of the upper lip to not form connectively. Because of

CL/P, patients are born with rather severe oral occlusions. There are three separate forms of the condition: unilateral incomplete, unilateral complete, and bilateral complete. When a patient has a unilateral incomplete cleft lip and palate, the cleft does not connect from the lip into the soft palate. If the patient's cleft connects from the lip to the soft palate, then the patient is diagnosed with a complete unilateral cleft lip and palate. However, if the patient's cleft connects from his soft palate to his lip, and splits in the hard palate to form two clefts in the lip, this is known as a bilateral cleft lip and palate. Although each individual CL/P case has a varying degree of severity, bilateral complete clefts are typically the most difficult to repair. These degrees of severity are based on a classification scale that includes most aspects of the patient's overall health, as well as his treatment regimen (Rajanikanth, B.R., *et. al*, 2012).

We can classify the severity of CL/P using man-made scales; however, the basis for determining the actual blueprints and causes of not only CL/P, is to follow the genetic markers laid out within DNA. Genetic markers are DNA sequences that are specific to every disease. Although the genetic markers responsible for CL/P have not been entirely determined, advances are being made in order to achieve this. A few genes under review are *GSTT₁*, *FGF₁₂*, *CX₄₃*, and *VAX₁*. These genes are all closely related to CL/P, but studies have not specifically linked them to the condition in an absolute way, or labeled them as a genetic marker. Labeling genetic markers simply states that the genes being labeled increase a person's likelihood of having the specific condition.

Although genetics play a key role in the manifestation of disease, certain environmental factors can also increase or decrease the likelihood of birthing a child with CL/P. For example, smoking tobacco products while pregnant can cause a defect in which the fetus lacks the *GSTT₁* gene (U.S. Department of Health and Human Services, 2007). This is believed to cause the

connective tissues not to form, and the child to have CL/P. Conversely, if a pregnant woman maintains a tobacco-free diet that is high in folic acid, which is found in most leafy green plants, the likelihood of birthing a child with CL/P drops significantly (Butali, Azeez, *et. al.*, 2013). In fact, in some nations, adding folic acid to a pregnant woman's diet lowered her risk of having a child with CL/P by approximately one-third (Wilcox, *et. al.*, 2007).

Despite the fact that the direct link between CL/P and other conditions has not yet been determined, family history studies have shown correlations between CL/P, and genetic hardships in close family members. In some small studies, it has been shown that there are some correlations between CL/P and genetic inclination to contract certain forms of cancer. The studies showed that there is a correlation between the presence of certain cancers in the immediate family members of CL/P patients (Lima, *et. al.*, 2013). Researchers specifically targeted five cancers, with the strongest correlation occurring in their study of colon cancer.

Along with hypotheses that state that a mother's diet can influence the likelihood of a child having CL/P, many researchers contend that the actual weight of a fetus can be directly correlated to whether or not the fetus has the condition (Kim, Min-A., *et. al.*, 2012). When a fetus is underweight, this typically corresponds to an overall poor health for the child. Although this has not been pinpointed exactly, physicians concluded that there was a correlation between the number of trips a pregnant mother visited her physician, and the health of the developing fetus (Lei, *et. al.*, 2013).

Accompanying the increased probability of contracting cancer, there are numerous other side-effects of CL/P. One such side-effect is, in actuality, a subset of CL/P known as Pierre-Robin Syndrome (PRS). PRS is a series of individual conditions that manifest simultaneously to

cause the larger collective condition (Selvi, R. *et. al.*, 2013). PRS is distinguished by three primary conditions: glossoptosis, which is an airway obstruction by the base of the tongue, micrognathia, which is a small jaw, and at least a cleft palate, if not CL/P. PRS is typically isolated, meaning that it is not found commonly. CL/P works similarly to PRS. When a patient is diagnosed with CL/P, the probability that they will contract several other defects increases (Kim, Min-A., *et. al.*, 2012). These can include minor defects, such as slight difficulties in swallowing, and speech impediments, or more severe defects such as chin deviation and alteration of facial morphology (Kim, Kyung-Seon, *et. al.*, 2013), and increased pressure on the neck and spinal column (Matulevičienė, Aušra, *et. al.*, 2013). The more severe defects are not as common and typically only occur in underdeveloped nations, globally.

Because gene sequencing cannot prevent CL/P, and a mother's prenatal diet alone will not prevent CL/P, so it must be treated medically. Physicians have been working to not only advance the classification of degrees of CL/P, but also to advance the surgical methods they employ to close the oral malocclusions caused by CL/P. The typical surgery includes trimming the tissues that surround the cleft, and then delicately sewing the two sides of the cleft together. Usually, this procedure occurs when the child is several months old. During the first several months of a child's life, the surface shape of the palate changes with the child's maturity and development. Therefore, by waiting to perform the procedure, the child's mouth will have already shifted into its more permanent form, making the surgery more likely to be successful. The surgeon will use very small stitches to close the cleft in an attempt to minimize scarring. The stitches also dissolve into the surrounding tissues over time. Although scarring is a side-effect that is avoided by surgeons, the main goal of the surgery is not to restore the appearance of a

patient, but to restore the functionality of a patient (Freitas, *et. al.*, 2013). The focus of surgery, as medicine advances, is to marry the concepts of functionality and aesthetics.

Although surgery is important, CL/P research is vital. The majority of research conducted on CL/P is conducted with little regard to the economic and environmental status of the regions from which the patients originated. Typically, research focuses on the etiological side of the CL/P, typically genetics. However, some studies have examined the patient's region of birth, the diet and habits of the mother prior to pregnancy and up to childbirth, the family's socioeconomic status, the immediate family genetics, and the family history. These studies demonstrated that the diet of the mother, as well as the immediate family genetics pinpointed the source of the CL/P (Acuna-Gonzalez, *et. al.*, 2011). Although it is difficult to trace the etiology of the genes responsible for CL/P, it has been shown that the usage of Folate as a prenatal supplement lessens the probability of CL/P (Butali, *et. al.*, 2013). Researchers stated that the purpose of these studies was to prove that a family's ability to access prenatal supplements could decrease the likelihood of a child having the condition. This fact caused these studies to take a turn away from genetic counseling and family planning, and direct emphasis towards poor socioeconomic status. The inability of a mother to access prenatal vitamins such as folic acid is most likely a factor in the increased incidence of CL/P in less-developed nations globally.

Because the majority of CL/P cases occur in underdeveloped nations, the families of CL/P patients are typically characterized by impoverished homes. These are the very people who cannot afford to pay for folic acid supplements, or reconstructive and reparative surgeries. Many families struggle under the extreme pressure of raising a child with CL/P. In these nations, the child often cannot receive the proper care they need, and usually are the product of unsuccessful surgeries. The stress of a CL/P patient is incredibly high, both physically and emotionally.

However, the life of a caregiver of a CL/P patient must be close to, if not equivalent to, that of the patient (Gowda, *et. al*, 2013.). A study was executed that provided a unique scope into the life of CL/P families in order to gain a fresh perspective on the quality of life of a caregiver of a CL/P patient. This was a pilot study, as most studies pertaining to CL/P are geared toward researching the patient. Using statistical analysis, researchers employed a General Health Questionnaire (GHQ) as a basis to determine the overall health of the patient's home life, from the perspective of the caregiver, who recorded their personal Mental Health (MH). The results strongly suggested that the caregivers suffered from poor MH overall. What little research had been conducted prior to that, suggested that the child's condition had nothing to do with the quality of quality of life (QOL) of the caregiver. The current research contradicted these older and obsolete concepts strongly, showing that caregivers of a certain demographic typically struggled with their QOL. These caregivers, specifically, were the mothers of young CL/P patients, typically infants. However, the results showed that the amount of time a caregiver spends with a CL/P patient is directly proportional to the caregiver's perception of their QOL. A caregiver who spends a great deal of time with the patient is more likely to value their life and have a positive outlook, seeing the importance of their role within the life of the patient. More studies like these should be conducted, as the future and hope of recovery of a CL/P patient depends greatly on the ability of a caregiver to perform their duties.

INTRODUCTION TO CASE STUDY

T.V. is a mutual CL/P patient of both Dr. Jen Orthodontics, and Coastal Carolina Oral and Maxillofacial Surgery. He is highly-intelligent young man, 11 years of age, and of Asian descent. The first time I was introduced to T.V., he looked up into my eyes from the orthodontic procedural chair, and then his eyes fell to the beard exploding from underneath and around my

dental mask. He remarked, “Why, hello, bearded man.” From the start, I knew T.V. would be an entertainingly different patient. T.V. was born with a congenital unilateral complete cleft lip and palate. He is an only child, with two extremely supportive parents; both of whom do not have CL/P. In fact, CL/P, as far as they know, does not run in his family, although the inclination is higher, due to the predisposition of his Asian genetics (Lei, *et. al.*, 2009). Apart from his condition, T.V. has no history of any major health issues. He enjoys all the things that normal children do: watching movies, playing video games—his condition does not hold him back. He enjoys eating a variety of food like tacos, pizza, and tofu. He finds no difficulty eating, even with his condition. He is currently on a non-restrictive diet, save restrictions placed on him by the orthodontic specialist. These restrictions are based on T.V.’s ability to chew due to his braces, and can be repealed at the patient’s choosing as long as he can chew safely, and painlessly. Though T.V.’s diet is unrestrictive, he does find hygiene somewhat of a chore at times. Braces are always difficult to clean, because bacteria can manifest in the cracks of brackets. However, due to T.V.’s unique situation, he has found that maintaining cleanliness can sometimes be more difficult than that of a “normal,” non-CL/P patient. Some CL/P patients suffer from soft enamel on their teeth. This is typical of patients in more developed nations because of the high levels of refined sugar and poor oral hygiene habits (De Moura, *et. al.*, 2013).

As a CL/P patient, and the recipient of CL/P reparative and reconstructive surgery, T.V. has had an intense regimen of procedures, both surgical and orthodontic. His surgery was both mechanical, as well as cosmetic. T.V.’s case is special. As his craniofacial features developed following his birth, T.V. endured an interesting developmental phenomenon. A typical child develops permanent teeth in the ridge of his upper oral arch between the ages of six and seven years. T.V., however, developed a permanent tooth which protruded at a sharp angle from the

center of his hard palate, instead of his upper oral ridge, due to his CL/P. Such teeth are coined “floaters.” These “floaters” are normal teeth that, because of their position pre-orthognatic surgery, fall extremely out of alignment with the rest of the oral ridge of the jaw when the gap is closed by CL/P surgical repair. When the gap is repaired, there is often a malocclusion of the upper and lower jaws. This means that the two separate jaws do not align as they are designed to. Due to his “floater,” T.V.’s malocclusion was quite unique (see Fig. 1). T.V.’s lower jaw, which was unaffected by his CL/P, was fairly aligned. However, a look at his upper jaw would reveal not only misalignment side-to-side, but also a misalignment forward to back. Unfortunately, the CL/P and surgical repair had caused a very unique case of alignment issues in T.V.’s mouth. Part of his jaw had an overbite, which occurs when the upper teeth hang too far in front the lower teeth; part of his jaw had an under-bite, which occurs when the upper teeth hang behind the lower teeth; and part of his teeth met as they were supposed to, with the upper teeth slightly in front of the lower teeth. These conditions made for quite a unique chimera of oral dilemmas (see Fig. 5).

T.V.’s CL/P was addressed by several orthognatic surgeries that were conducted when he was a baby and toddler; however, his “floater” could not be fixed via surgery (see Fig. 3). Because the cleft was closed, leaving the “floater” suspended in the center of his hard palate, the tooth had to be addressed through the simple principles of orthodontic physics. When T.V. was about ten years old, braces were applied to his teeth as they would be to a normal patient (see Fig. 4). Following the application of braces, an orthodontic bracket was centered and cemented onto the lateral face of the “floater.” The orthodontic specialist tied a high-test orthodontic rubber band into the bracket on the “floater,” and linked this into the wire of the braces. Over

time, with the constant pulling pressure of the orthodontic rubber band, T.V.'s "floater" was pulled into place, and his malocclusion was aligned.

CONCLUSION

The future for T.V., and other CL/P patients, is bright. Numbers are diminishing in developed nations, due to education on the importance of avoiding tobaccos products, and controlling the consumption of alcohol—especially for pregnant women. Also, with research increasing both on the preventive front, as well as the reparative front, the numbers are expected to decrease in underdeveloped nations over time. Studies in the benefits of folic acid supplements as well as surgical procedural improvements have aided in the overall decrease in number of cases. Improvements include using techniques such as Cone Beam Tomography (Choi, *et. al.*, 2013). Cone Beam Tomography(CBT) maps out the tissues of the oral cavity, allowing surgeons to gauge the tissue volume prior to and following, surgery. This allows them to cut more precisely, where the tissue is thick, and not risk the chance of a tissue tear. CBT makes surgeries more effective, and shortens rehabilitation time. Although physicians would love to see the length of rehabilitation shortened, that is not their primary goal. Their primary goal is simply to rehabilitate to optimal health, regardless of the time it takes. Because of this, some emerging options for orthognathic surgery include osteogenesis (Rao, *et. al.*, 2013). The purpose of this kind of surgery is to use the anterior segmental distraction osteogenesis, which is a lengthening of the jawbone, to improve the aesthetic balance of the face and provide a healthy occlusion. Typically, orthognathic surgery can be highly complex with many side-effects, followed by a difficult recovery period. However, anterior segmental distraction osteogenesis

can provide a solution to all of the typical issues of CL/P, including a restoration or preservation of the patient's phonetics. Speech therapy is usually required after major CL/P reparative surgeries, although most phonetic restoration occurs due to a realignment of the oral occlusion. The surgery allows the teeth to be properly aligned and thus causes a strengthening of a patient's speech abilities.

CL/P is a congenital condition with a genetic predisposition. In other words, no one ever asks for it, or does anything to earn it. Its incidence can be decreased by expecting mothers making healthy choices, although all risks cannot be eliminated. After looking at T.V.'s case, it is obvious that modern medicine is having an impact on the lives of CL/P patients: improving their livelihood, and allowing them the opportunity to be rehabilitated toward normalcy. Modern medicine is effectively bridging the gap between what was once a hopeless condition, and is today something fixable. T.V.'s orthodontic alignments should be complete by the end of the year. Now *that* is a reason to smile.

Figures

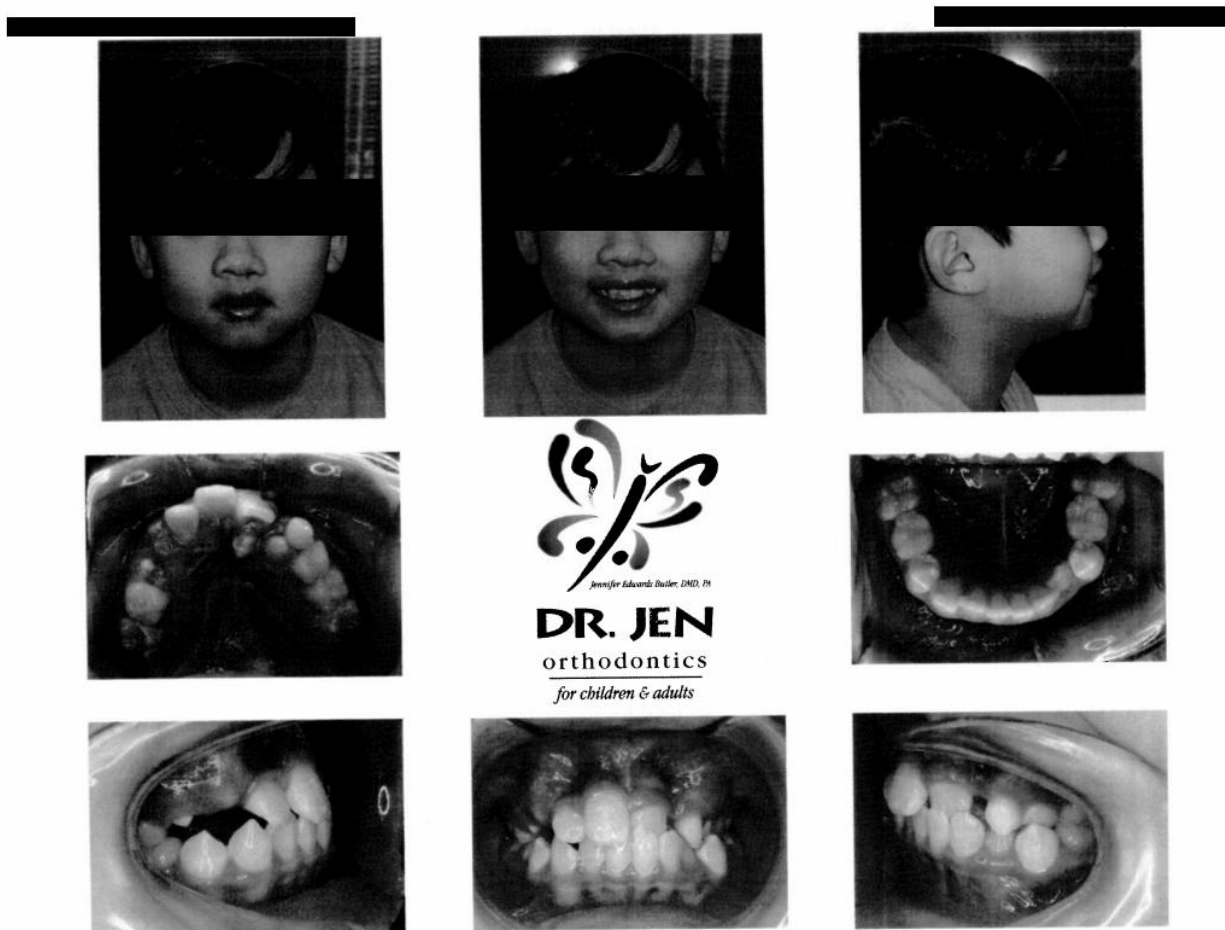


Figure 1: T.V. First Progression Photos (04/12/2012): it is clear that T.V.'s front incisors are either in an overbite, underbite, or healthy occlusive position.



Figure 2: T.V. Second Progression Photos (09/12/2013): after a year of pressure from the braces, we can see some of the gaps in T.V.'s front incisors closing, as well as the alignment of the jaws coming together to form a healthy occlusion.



Figure 3: T.V. Pan X-Ray from 03/13/2012, prior to application of braces: here is another view of the tooth positioning prior to application of braces. Note the angle of the floater, in the upper jaw behind the front incisors.



Figure 4: T.V. Pan X-Ray from 07/23/2012, following application of braces: this is a view of the mouth after application of braces. You can see the angle of the “Floater” becoming sharper as it is pulled into alignment with the teeth of the upper ridge.

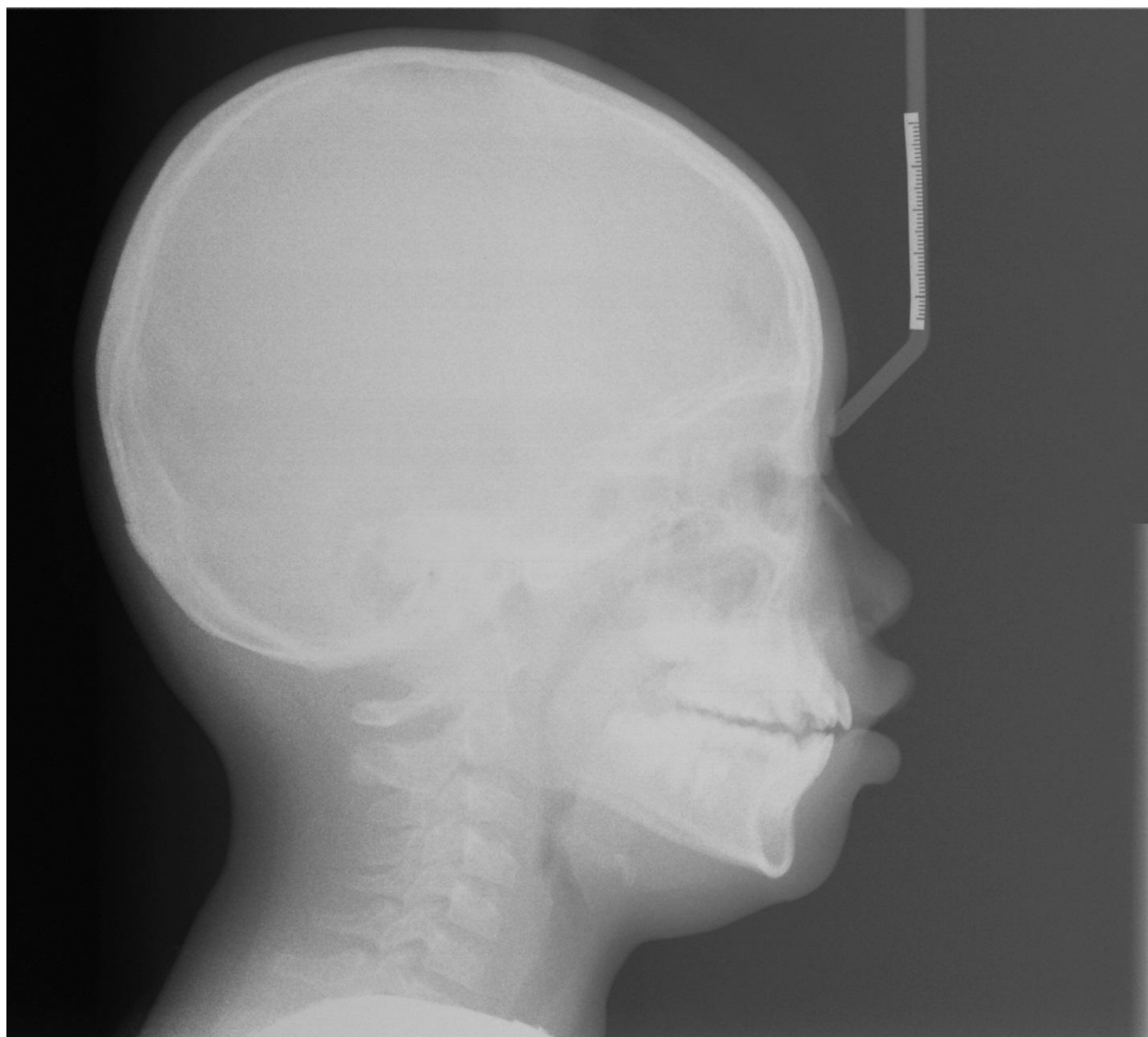


Figure 5: T.V. Ceph. Examination from 04/17/2012: this is a full head scan, revealing the shape of T.V.'s jawline prior to the application of braces. Note the malocclusion of the lower and upper jaws, especially around the front incisors, and the canine regions.

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