EDITORIAL

Evoked potentials and Chiari malformation Type 1**P. David Adelson, MD**

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CHIARI malformations (CMs) are well-known structural defects that most often consist of downward displacement of the cerebellar tonsils through the foramen magnum, causing either obstruction of CSF or compression of the brainstem. Because of the significant variability in the structure of the posterior fossa (PF) and related congenital anomalies, there have been a number of different classification subtypes that have been described. Initially, there were 4 subtypes delineated that were related to different anomalies of the brain and hindbrain as well as other associated features. CM Type 1 (CM-1) is the most common and has been defined as cerebellar tonsillar descent of greater than 5 mm. Two further subtypes have been more recently described, including Type 0 (CM-0, lack of cerebellar herniation with or without syringomyelia) and Type 1.5 (CM-1.5, brainstem and tonsillar herniation). These different structural anomalies may result in symptoms related to the obstruction of CSF and/or compression, such as headaches aggravated by Valsalva maneuvers, vertigo, dizziness, etc., or to injurious changes in the spinal cord (specifically signal changes on imaging, or worse, syringomyelia) that may be asymptomatic or symptomatic, i.e., pain, weakness, or numbness in the back, arms, or legs. CM is believed to be fairly prevalent (1–3/1000 births), and women are 3 times more likely to have CMs compared with men.¹ However, with our society's frequent use of imaging for minimal or unrelated symptomatology, the incidental diagnosis of CMs has become more common.

CM Types 3 and 4 are rare, and it is abundantly clear as to their specific and related deficits. Type 2 is by definition accompanied by a myelomeningocele, with a number of other congenital anomalies frequently associated with this syndrome. These different subtypes have different presentations and have specific criteria for intervention.

For the rest of the different subtypes, the decision-making involved for proceeding with surgery may vary from surgeon to surgeon, but for the most part there have been two criteria that have served as justification for surgical intervention: 1) a symptomatic syndrome of headache and associated other symptoms interfering with quality of life; or 2) significant (frequently defined as > 3 mm in diameter) and/or progressive syringomyelia with or without symptoms. For CM-0, CM-1, and CM-1.5, however, the challenge is defining objective criteria for surgical intervention for the vast majority of those that are found incidentally.

In this issue, Moncho and colleagues² utilize a prospectively collected, retrospectively reviewed cohort of 200 adolescent and adult patients (from an overall cohort of almost 550 patients) with CM-0, CM-1, and CM-1.5 over a 9-year period who had preoperative electrophysiological studies as part of their “routine workup” for symptomatic and asymptomatic CMs. Their objective was to begin to define the relationship between preoperative electrophysiological studies—including brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials (SSEPs)—and the clinical findings, associated abnormalities in patients with syringomyelia, and the clinical and neuroradiological risk factors in CM. They also obtained normative data from 50 healthy volunteers that were age-, sex-, and height-matched controls and that had been previously published by the authors. These authors found that 60% of their patients showed alterations in electrophysiological recordings with variable differences between the different subtypes, findings of syringomyelia, and whether the CM was discovered incidentally.

While there is no question that CM-0, CM-1, and CM-1.5 likely represent a continuum of structural findings and variability of compression and/or obstruction of CSF out-

flow, previous studies and commentaries have led to the present classification scheme and definition of the different subtypes of CM. There is also some confusion that despite the fact that more than 40% of the cohort was patients with CM-0 and CM-1.5, there is a focus on CM-1, based on the title of the paper. Obviously, there is more recent literature suggesting the specific reasons for these new subtypes of CM and unless there is new evidence indicating such, they should not be represented as subtypes of CM-1. Using the current literature, it is also difficult to interpret the validity of the extent of tonsillar herniation, whether 3 mm or 5 mm, to define the specific CM subtype. The authors have chosen 3 mm as their cutoff to define their subtypes, which may confuse what ultimately is the issue, that of obstruction and/or compression. By making this choice, they lessen the size of the cohort of patients with CM-0, a subtype that remains controversial as to its existence and/or its significance, creating a very small subgroup for analysis. Similarly, because not all patients with CM-1.5 underwent electrophysiological studies that indicated compression, this may represent a different pathological finding as well as a different indication for surgical intervention. Additionally, it is unclear how an asymptomatic patient with CM-0 and no syringomyelia would even need to undergo electrophysiological studies and then potentially have a surgical indication for intervention if the electrophysiological studies were “abnormal.”

While this study has attempted to answer the question that electrophysiological studies can provide added information, especially to patients with incidental findings of CM, and despite the normative electrophysiological data provided, it is well recognized that there can still be significant variability and subjectivity from electrophysiological study to electrophysiological study technically in how the study is completed and interpreted, resulting in differences within the same patient, variability in response from one patient to the next, and variability in the interpretation of clinical “significance” by the neurophysiologist. Because of this significant variability, it would be very difficult to conclude that a single electrophysiological abnormality, either BAEP or SSEP (especially if not impacting both), indicates a high probability of progression of disease and/or being able to define the damage to the spinal cord either with or without syringomyelia. The literature is replete with studies of the clinical impact of abnormal electrophysiology that have been quite variable and inconsistent, especially related to surgical decision-making. While a study such as the one by Moncho et al. in this issue helps to define abnormality at any given point in time, it still does not indicate “damage” or progression of disease. We must be careful in this type of interpretation because these patients do not have a baseline to make comparisons longitudinally in the preoperative setting to be able to state definitively that there is progression or further damage, as no repeated studies were conducted. Particularly if we were going to define surgical indication based on “progression,” longitudinal and progressive abnormality of the electrophysiological studies would need to be defined.

Lastly, as the authors concur, this study suffers from

being a retrospective review, even though they utilized a prospectively collected cohort. Ultimately, this was just a clinical registry of patients with CMs since it lacked a prospective set of criteria for inclusion, exclusion, diagnosis, management and/or assessment of outcome. Future studies should consider other methods for optimizing the prospective collection of data so as to optimize the eventual conclusions. While a prospective clinical registry can be quite useful to begin to raise new clinical questions, if specific hypotheses for diagnosis, management, and outcomes are not delineated up front, then the data do not provide sufficient power to answer specific clinical questions (such as posed in this study) and provide understanding as to the nuances of a particular diagnosis and its management. This study highlights this weakness because the data were collected over a 9-year period, the indications for obtaining electrophysiological studies are not clearly indicated or delineated, and as a result it is unclear why almost two-thirds of the patients did not obtain these studies as part of the routine workup, as the number of physician decision-makers and the evolution in their thinking would have to be considered as to the number and types of patients receiving the diagnostic studies. Similarly, it is presumptive to be able to conclude that there was no further assistance of these studies in the surgical indication and ultimately surgical decision-making without understanding the bias in the patient selection criteria for obtaining these studies as part of this routine diagnostic evaluation, and then ultimately what were the indications for surgical intervention.

Overall this is a well-done, large, retrospective study that further contributes to our understanding of the pathophysiology of adult CM and syringomyelia. It also begins to suggest a potential clinical pathway for the evaluation and then decision-making for surgical intervention in patients with these incidentally found lesions utilizing electrophysiological studies, which should be further explored. Obviously, defining a clinical pathway for this diagnostic evaluation with specific indications, and then performing a prospective, hypothesis-driven clinical study to establish objective evidence for the diagnosis of subclinical dysfunctions and actual neurological progression, as well as the surgical indications for these patients, would be useful.

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References

1. Milhorat TH, Bolognese PA, Nishikawa M, McDonnell NB, Francomano CA: Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation Type I in patients with hereditary disorders of connective tissue. **J Neurosurg Spine** 7:601–609, 2007
2. Moncho D, Poca MA, Minoves T, Ferré A, Cañas V, Sahuquillo J: Are evoked potentials clinically useful in the study of patients with Chiari malformation Type I? **J Neurosurg** [epub ahead of print April 15, 2016]. DOI: 10.3171/2015.11.JNS151764]

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Response

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We would like to thank Dr. Adelson for his editorial and thoughtful critique of our paper. We also appreciate the opportunity to expand on the topics raised in the editorial that are relevant to clinicians who manage patients with CMs. For the sake of clarity, we have divided our responses into 3 main issues that the editorial raised: 1) traditional and new criteria for the classification of CMs, 2) the reliability of evoked potentials (EPs) and their clinical usefulness, and 3) methodological issues and the applicability of our findings.

Traditional and New Criteria for the Classification of CMs

Dr. Adelson notes that in our study, “There is also some confusion that despite the fact that more than 40% of the cohort was patients with CM-0 and CM-1.5, there is a focus on CM-1, based on the title of the paper.” The primary reason that we decided to use the term CM Type 1 (CM-1) in the title was that, in our opinion, the new 6-tier classification introduced by Tubbs et al.^{11,13} allows for a much better stratification of the different patients traditionally included within the broad term of CM. The classification of Tubbs et al. basically adds 2 additional categories to the classic 4-tier classification: CM Type 0 (CM-0) and CM Type 1.5 (CM-1.5).¹² However, this new nomenclature has not yet gained wide acceptance. Therefore, some authors (including the referees of some journals) prefer to use the original classification and use the terms CM-1 to refer to traditional tonsillar herniation (with variable thresholds) and CM Type 2 (CM-2) to describe hindbrain abnormalities found in patients with neural tube defects. Following the traditional nomenclature, all but 14 patients of the total cohort of 200 included in our study had CM-1. Indeed, patients with CM-1.5 were reclassified in 2013 after we re-examined the MR images of all patients included in our study and applied the neuroradiological criteria described by Tubbs et al.¹³ Readers interested in the classic terminology may refer to the figures for the total cohort summarized in Tables 1–3 of our paper; readers who are curious about the new classification are encouraged to view the split data shown in the same tables. All patients with CM-1.5 would fall within the CM-1 category according to researchers who prefer the traditional classification. We believe that the primary message of our paper is not distorted by using this dual approach. In addition, we do not believe that the 14 patients with CM-0 that we described (7% of our cohort) introduced any significant bias to our findings, particularly because the type of CM was included as a covariate in our logistic regression analysis.

A second concern Dr. Adelson raises is that we used 3 mm as the cutoff to define the CM subtypes. His comment is that this cutoff “may confuse what ultimately is the issue, that of obstruction and/or compression.” Dr. Adelson is correct; we could have used a 5-mm cutoff and not the 3-mm cutoff. However, both thresholds are arbitrary, and there is no robust evidence to support the use of either one. In fact, the 3-mm threshold that we chose has been “written in stone” in the neuroradiological literature since the seminal paper published by Barkovich et al. in 1986.² Many patients are referred to a neurosurgeon after MRI is conducted on the basis of persistent headaches. A CM is described in the neuroradiological report, again based on an arbitrary cutoff. However, the primary reason that we selected a 3-mm cutoff, representing “minimal” tonsillar ectopia, is the increasing evidence that CM is primarily an axial mesodermal developmental anomaly that results in a small PF. This hypothesis is based on 3 main lines of evidence: 1) experimental studies conducted by Marín-Padilla in which occipital bone undergrowth and cerebellum displacement was induced by giving vitamin A to pregnant hamsters;^{7,8} 2) morphometric studies in patients with CM-1 that corroborated the overcrowding of a normally developed hindbrain within a hypoplastic PF^{6,14} as the main etiopathogenic cause; and 3) the fact that different surgical techniques that increase the volume of the PF ameliorate the majority of symptoms and resolve the associated syringomyelia.¹⁰ This evidence does not support the reductionist approach of selecting any arbitrary threshold to define CM. Dr. Adelson emphasized that different types of CM likely represent “a continuum of structural findings.” In this context, it is easy to understand why some patients with CM and tonsillar herniation between 0 and 5 mm may have significant syringomyelia that improves after PF surgery. Indeed, this rationale prompted Iskandar et al. to introduce the controversial CM-0 type in the CM nomenclature.⁵

In summary, clinical and neuroradiological findings from the last two decades suggest that any degree of tonsillar herniation below the level of the foramen magnum should be considered to be a surrogate variable for a crowded PF. As a consequence, many CM researchers believe that even a minor ectopia of the cerebellar tonsils in the presence of a crowded PF—indicated by an absent cisterna magna—might be suggestive of a minor form of CM. Although the CM-0 type remains controversial, restricting the definition of CM to an arbitrary descent of the tonsils below the level of the foramen magnum is misleading and likely incorrect. In a previous study, we showed that a mathematical model combining 7 morphometric measures, regardless of the degree of tonsillar herniation, was able to correctly discriminate—with a high sensitivity and specificity—between patients with CM-1 and control patients.¹⁴ In agreement with previously published data, the patients in our present study also exhibited radiological signs of an underdeveloped PF with a significant shorter clivus length, a reduced sagittal PF area, and a more acute tentorium–occipital bone angle.

Dr. Adelson puts forth the notion that our patients with CM-1.5 (49 cases), 34.4% of whom did not have syringomyelia and 41.2% had a syrinx, had completely normal EPs. As a result, he comments that “because not all pa-

tients with CM-1.5 underwent electrophysiological studies that indicated compression, this may represent a different pathological finding as well as a different indication for surgical intervention.” We too were disappointed by the low frequency of neurophysiological abnormalities found in patients with CM-1.5. However, the definition of CM-1.5 is based on its phenotype—defined by MRI—and not by any neurophysiological abnormality. In their analysis of 22 pediatric patients with CM-1.5, Tubbs et al. remarked that the primary difference between CM-1.5 and CM-1 cases is that tonsillar herniation in the former is associated with a variable degree of caudal descent of the brainstem evaluated on sagittal MRI by a displaced obex beneath the basion-opisthion line.¹³ This hindbrain herniation is typically confirmed at surgery and defines a more severe distortion of the rhombencephalon. In our patients with CM-1.5, we did not find any significant difference with the other two groups in the mean age at diagnosis or the age of symptomatic onset. The only significant difference that we found was that syringomyelia was less frequent in this group than in either of the other two groups. CM-1.5 shares some anatomical distortions also found in CM-2, but whether or not this phenotype has a different natural evolution or more severe brainstem symptoms such as sleep disorders, hypopneas/apneas, etc., requires a different study design and a cohort with a larger number of patients. Based on our experience, surgery in patients with CM-1.5 is sometimes challenging because of the severe distortion of the brainstem, the more frequent finding of arachnoiditis, and the frequent need for subpial resection of the tonsils to adequately restore the normal CSF dynamics at the level of the craniovertebral junction.

Dr. Adelson believes that our study was not clear enough either in the workup or in the surgical indications for patients with CM-0. He comments that it is unclear “how an asymptomatic patient with CM-0 and no syringomyelia would even need to undergo electrophysiological studies and then potentially have a surgical indication for intervention if the electrophysiological studies were ‘abnormal.’” Our routine workup for any symptomatic patient with CM or asymptomatic patients with syringomyelia at our institution is to admit them to our department to complete all of the required neuroradiological and neurophysiological examinations. As described in our paper, in this short admission, all patients, regardless of the severity of their symptoms, undergo all neuroradiological studies, EP studies, and polysomnography to rule out apneas/hypopneas. Our criteria for recommending surgery are very similar to those that Dr. Adelson notes in his introduction and are based on clinical parameters and the neurological examination. One additional indication for surgery that we have established is the finding of a sleep apnea/hypopnea syndrome in otherwise oligosymptomatic or asymptomatic patients. Consequently, the EP results are never used in isolation to indicate or exclude surgical treatment.

The Reliability of EPs and Their Clinical Usefulness

Another important issue that Dr. Adelson raises is the significant inter- and intraobserver variability that EPs may have. He states that despite the normative EP data we provided in our study, “it is well recognized that there

can still be significant variability and subjectivity from electrophysiological study to electrophysiological study technically in how the study is completed and interpreted, resulting in differences within the same patient, variability in response from one patient to the next, and variability in the interpretation of clinical ‘significance’ by the neurophysiologist.” With all due respect to the Dr. Adelson, we believe that this point is not correct and merits clarification. In our study, EPs were always conducted in the same laboratory following the accepted international guidelines referred to in the *Methods* section and by the same staff (D.M. and T.M.), both of whom possess considerable expertise in this field. Dr. Adelson and potential readers may question if our approach has external validity and therefore can be extrapolated to patients in real-world situations. We believe that our findings can be easily generalized to any institution with a neurophysiology department that follows the guidelines published by the American Clinical Neurophysiology Society on EPs.¹ According to these guidelines, and under the heading “Recommended Qualifications for Interpreters of Clinical Evoked Potential Studies,” the text reads “Becoming credentialed by a national examining organization, assessing adequacy of knowledge of evoked potentials, is the only objective method of demonstrating competency in interpretation of clinical evoked potential studies.”¹ Therefore, we believe that under standard conditions for EP equipment, qualified technologists, accredited interpreters, and normative data, our data should be reproducible elsewhere with minimal interobserver disagreement and nonsignificant inpatient variability.

The reliability of EP studies also received an unfavorable judgment from the editorial writer. Dr. Adelson affirms that “the literature is replete with studies of the clinical impact of abnormal electrophysiology that have been quite variable and inconsistent, especially related to surgical decision-making.” While we agree with Dr. Adelson that the literature contains plenty of case reports, to our knowledge, only a few studies—all with very limited and heterogeneous series of patients—have described the findings of BAEPs and SSEPs in CM. With the exception of our preliminary article published elsewhere,⁹ most studies (noted in our paper) included fewer than 28 patients. Based on the analysis of a large cohort, we aimed to answer some of the questions regarding the role of EPs in the diagnosis of the CM and their relationship with both the clinical findings and the severity of the malformation.

Dr. Adelson correctly warns that “while a study such as the one by Moncho et al. in this issue helps to define abnormality at any given point in time, it still does not indicate ‘damage’ or progression of disease.” We agree with his opinion. Our study helps to define abnormalities only at a given point in time, but it does not allow researchers to draw conclusions regarding the potential progression of the disease. Our study was designed as a cross-sectional study, and therefore its primary purpose was to provide a “baseline” description of the BAEP and SSEP abnormalities found in a large cohort of patients, data that surprisingly have not been previously described. Therefore, our study should be considered a starting point on this subject; it represents a broad descriptive approach with neurophysiological information that has not been reported

thus far. This information is necessary before designing any prospective study regarding the sensitivity, specificity, and predictive values of EPs for detecting patients who may improve after surgery or in whom a progression of the disease is expected. In addition, we described for the first time BAEP and SSEP findings in asymptomatic patients over the entire CM spectrum, except for CM-2. We fully agree with Dr. Adelson that determining whether or not EPs can predict the natural evolution of the disease requires additional research ideally conducted over multiple centers.

Methodological Issues and the Applicability of Our Findings

In the last part of his editorial, Dr. Adelson addresses some of the methodological issues that our study raises. The first issue that he notes is the limitation of the “retrospective nature” of our cohort. The editorial writer says that “this study suffers from being a retrospective review, even though they utilized a prospectively collected cohort. Ultimately this was just a clinical registry of patients with CMs since it lacked a prospective set of criteria for inclusion, exclusion, diagnosis, management and/or assessment of outcome.” We believe that this criticism is unfair, and we wish to make a few statements to ensure that other clinical researchers are not deterred from investing time and effort in collecting high-quality information that only patient-centered registries can offer. Traditionally, retrospective designs have had a bad reputation in science. For many researchers, the caricature of a retrospective clinical study is a group of residents and research nurses digging into paper- or electronic-based medical records to find data that never were there. It is true that missing and poor-quality data have plagued these studies in the way they were conducted in the past. As a consequence, in the hierarchy of evidence, retrospective studies are always at the bottom of the pyramid. However, the situation has changed dramatically in the last decade, and it has been shown that randomized clinical trials (RCTs) are not always possible, can be of poor quality, are subjected to different sources of bias, and might have very low external validity. In addition, some research questions do not permit random assignment of the participants; in some cases, randomly placing participants in groups would be considered unethical. Even when RCTs are feasible, they are not designed to provide some of the answers researchers are looking for in studies of a rare disease such as CM. In this scenario, well-designed clinical registries are powerful tools for conducting high-quality clinical research. Patient registries employ a prospective observational study design that does not specify treatments or require any therapies intended to change patient outcomes.⁴ Patients are typically included in registries when they present for care.

Our CM registry is basically a single-institution patient registry in which all patients admitted to our institution with a diagnosis of a CM and the criteria noted in the previous section are included. For each patient, we record a core data set that includes all known clinically relevant information, the results of neurological and neuroradiological examinations, health-related quality of life variables, standardized outcome data, and blood samples collected

for potential genetic studies. The registry has a dictionary with a consistent definition of variables. The majority of patients have a follow-up period of at least 5 years, and the participant attrition rate is very low. This electronic registry was planned with the purpose of determining the long-term outcomes of the “posterior fossa reconstruction” technique that we proposed in 1994.¹⁰ All outcomes are evaluated by the patient and the surgeon in charge. Health-related quality of life parameters are always independently evaluated by a research nurse or a neuropsychologist not directly involved in the patient’s clinical management. Our registry is subjected to periodic quality controls. Needless to say, many variables and new scales have been added to the registry since its original implementation. However, the date when the variable was added was recorded and is only used prospectively. Genetic studies have been conducted in some of these patients, and the results have been published elsewhere. For all these reasons, we do not share Dr. Adelson’s belief that our data “do not provide sufficient power to answer specific clinical questions (such as posed in this study).” We hope that the clarifications we have presented will convince Dr. Adelson that we have used the right tool to answer the right question.

In addition, we wish to emphasize that advances in biostatistical methods have recently broadened the scope of questions that can be addressed using well-designed clinical registries. Stratification, propensity score matching, and risk adjustment are statistical methods that can be used to address confounding, control for bias, and creating homogeneous subgroups for analysis. However, statistical strategies for mining clinical registries can only be applied to high-quality data sets, and data mining these data sets can be compared to mining for gold. However, applying these methods to poor-quality data is equivalent to digging in a trash bin. Therefore, planning, designing, curating, and maintaining up-to-date patient registries are essential components of modern, good clinical research. The most important limitation of our registry is its single-institution database with a strong referral pattern for patients with CMs. Therefore, our registry represents a highly selected series of cases with a highly biased mode of management and treatment. Ideally, patient-centered registries need to be multicentric, a design that is the key for the new controversial comparative-effectiveness research initiatives.³

Dr. Adelson questions our conclusion that “there was no further assistance of these studies in the surgical indication and ultimately surgical decision-making without understanding the bias in the patient selection criteria for obtaining these studies as part of this routine diagnostic evaluation, and then ultimately what were the indications for surgical intervention.” We hope that we have been able to clarify the potential biases in our study. However, we still maintain that our data are sufficiently robust to extract the conclusions that we did. Again, we were disappointed with our findings that the EPs were not better than the traditional neurological examination in symptomatic patients with CM. A larger percentage of patients with CM-1.5 presented with abnormal BAEPs, even in patients without syringomyelia, but all of them were clinically symptomatic and had abnormal neurological examinations (see Fig. 2 in our paper). As we discussed, determining whether or not EPs are useful in the workup of CM needs to be placed

in a clinical context. In clearly symptomatic patients or in patients in whom syringomyelia induces severe symptoms (e.g., sensory loss and motor weakness), our findings suggest that both BAEPs and SSEPs do not add any clinically relevant information. Therefore, except for clinical research or very carefully selected patients in whom the progression of the disease needs to be confirmed, classic EPs do not need to be included in the routine workup of CM.

An important finding in our series was that 23 patients in a cohort of 46 asymptomatic individuals in whom CM had been discovered incidentally exhibited abnormal EPs. The importance of this finding and the predictive value of these abnormal findings to predict the natural evolution of the disease cannot be inferred and necessitates additional studies or the extraction of data over a long-term follow-up for the patients already included in our clinical registry. Again, we believe that a high-quality clinical registry—ideally multicentric and multinational—is the most powerful tool to definitively answer this clinically relevant question.

References

1. American Clinical Neurophysiology Society: Guideline 9A: Guidelines on evoked potentials. **J Clin Neurophysiol** **23**:125–137, 2006
2. Barkovich A, Wippold F, Sherman J, Citrin C: Significance of cerebellar tonsillar position on MR. **AJNR Am J Neuroradiol** **7**:795–799, 1986
3. Curtis JP, Krumholz HM: The predicament of comparative effectiveness research using observational data. **Annals Intern Med** **163**:799–800, 2015
4. Gliklich RE, Dreyer NA, Leavy MB: **Registries for Evaluating Patient Outcomes: A User's Guide**, ed 3. Rockville, MD: US Department of Health and Human Services, Agency for Healthcare Research and Quality, 2014
5. Iskandar BJ, Hedlund GL, Grabb PA, Oakes WJ: The resolution of syringohydromyelia without hindbrain herniation after posterior fossa decompression. **J Neurosurg** **89**:212–216, 1998
6. Karagoz F, Izgi N, Kapijcioglu Sencer S: Morphometric measurements of the cranium in patients with Chiari type I malformation and comparison with the normal population. **Acta Neurochir (Wien)** **144**:165–171, 2002
7. Marín-Padilla M: Notochordal alterations in axial skeletal-neural dysraphic disorders. **Virchows Arch A Pathol Anat Histopathol** **422**:97–98, 1993
8. Marín-Padilla M, Marín-Padilla T: Morphogenesis of experimentally induced Arnold-Chiari malformation. **J Neurol Sci** **50**:29–55, 1981
9. Moncho D, Poca MA, Minoves T, Ferre A, Rahnama K, Sahuquillo J: Brainstem auditory and somatosensory evoked potentials in relation to clinical and neuroimaging findings in Chiari type I malformation. **J Clin Neurophysiol** **32**:130–138, 2015
10. Sahuquillo J, Rubio E, Poca MA, Rovira A, Rodriguez-Baeza A, Cervera C: Posterior fossa reconstruction: a surgical technique for the treatment of Chiari I malformation and Chiari I syringomyelia complex—preliminary results and magnetic resonance imaging quantitative assessment of hindbrain migration. **Neurosurgery** **35**:874–885, 1994
11. Tubbs RS, Elton S, Grabb P, Dockery SE, Bartolucci AA, Oakes WJ: Analysis of the posterior fossa in children with the Chiari 0 malformation. **Neurosurgery** **48**:1050–1054, 2001
12. Tubbs RS, Griessenauer CJ, Oakes WJ: Chiari malformations, in Albright AL, Pollack IF, Adelson PD (eds): **Principles and Practice of Pediatric Neurosurgery**, ed 3. New York: Thieme, 2014, pp 192–204
13. Tubbs RS, Iskandar BJ, Bartolucci AA, Oakes WJ: A critical analysis of the Chiari 1.5 malformation. **J Neurosurg** **101** (2 Suppl):179–183, 2004
14. Urbizu A, Poca MA, Vidal X, Rovira A, Sahuquillo J, Macaya A: MRI-based morphometric analysis of posterior cranial fossa in the diagnosis of Chiari malformation type I. **J Neuroimaging** **24**:250–256, 2014