AJNR

Hyperintense signals of the posterior lobe of the pituitary gland on MR images.

I Fujisawa, R Asato and M Kawata

AJNR Am J Neuroradiol 1989, 10 (6) 1280-1282
http://www.ajnr.org/content/10/6/1280.citation

mainly the hypoglossal and dorsal vagal nuclei. The conclusion was as follows: "This suggests that the observed cranial nerve dysfunction in infants with the Arnold Chiari malformation *may*, at least in some cases, be secondary to an absence of adequate neuronal structures and thus unresponsive to posterior decompression procedures " [4]. Nowhere do Gilbert et al. directly or indirectly infer that this is the most likely cause for symptomatology.

Second, Wolpert et al., on analysis of their patients for the level of medullary kink, found symptomatic patients with medullary kinks well above C4 as well as asymptomatic patients with medullary kinks below C4. With regard to the asymptomatic group, we have observed several children who went for months or years without the development of typical symptomatology only to have life-threatening respiratory distress or worsening spasticity later. Next, with respect to the outlying symptomatic patients, the criteria for inclusion in the symptomatic group in our series were relatively rigid [5], and in 11 of 12 patients, symptoms were severe enough that surgery was offered.

Third, Wolpert et al. state that their data substantiate their original contention that the level of the medullary kink cannot be used to identify those children who may benefit from surgery. We find no indication in their article [1] that the level of the medullary kink was determined, although they did assess brainstem herniation by relating the position of the midbrain and pons to the sella and foramen magnum, and they did grade the cervicomedullary deformity.

In summary, we think that MR is helpful in identifying those patients in whom development of clinical symptomatology because of hindbrain herniation is likely, particularly if the medullary kink is at C4 or lower. Because the morbidity and mortality associated with surgical treatment of these patients are low, and because numerous articles have reported the reversibility of lethal symptoms in some children who had surgery, we continue to offer this operation to families of infants who have cranial nerve signs and symptoms, when our rigid clinical criteria for surgery are present [5]. Our experience with children whose progressive symptom is spasticity is most encouraging, and without reservation we continue to recommend neurosurgical intervention for this group. Although we think that MR is and will continue to be extremely helpful in the management and preoperative evaluation of these patients, the decision to operate must be based first and foremost on the clinical status of the patient. Our results suggest that patients with a more severe hindbrain hernia should be followed more closely for the development of symptomatology, and that if a decompression is performed, the decompression laminectomy should extend below the level of the hernia.

John T. Curnes
Greensboro Radiology Associates
Greensboro, NC 27415
W. Jerry Oakes
Orest B. Boyko
Duke University Medical Center
Durham, NC 27710

REFERENCES

1. Wolpert SM, Scott RM, Platenberg RC, Runge VM. The clinical significance of hindbrain herniation and deformity as shown on MR images of patients with Chiari II malformation. *AJNR* **1988**;9:1075–1078
2. Wolpert SM, Anderson M, Scott RM, et al. Chiari II malformation: MR imaging evaluation. *AJNR* **1987**;8:1037–1044
3. Curnes JT, Oakes WJ, Boyko OB. MR imaging of hindbrain deformity in Chiari II patients with and without symptoms of brainstem compression. *AJNR* **1989**;10:293–302
4. Gilbert JN, Jones KL, Rorke LB, Chernoff GF, James HE. Central nervous system anomalies associated with meningomyelocele, hydrocephalus and the Arnold-Chiari malformation: reappraisal of theories regarding the pathogenesis of posterior neural tube closure defects. *Neurosurgery* **1986**; 18:559–564
5. Oakes WJ, Worley G, Spock A, Whiting K. Surgical intervention in twenty-nine patients with symptomatic type II Chiari malformations: clinical presentation and outcome. *Concepts Pediatr Neurosurg* **1988**;8:76–85

Hyperintense Signals of the Posterior Lobe of the Pituitary Gland on MR Images

We were astonished by some of the findings in the experimental study on the hyperintense signal (HIS) of the posterior lobe of the pituitary gland on T1-weighted MR images reported by Kucharczyk et al. [1] in the November/December 1988 issue of *AJNR*. As may be known, some controversy about the source of this signal has arisen between the group at the University of California, San Francisco (UCSF), and us [2, 3]. In 1987 [4], we first reported that the HIS is absent in patients with diabetes insipidus and subsequently hypothesized that this signal reflects functional integrity of the hypothalamic-neurohypophyseal system and probably is indicative of neurosecretory granules (NSGs) containing antidiuretic hormone (ADH). Recently, the UCSF group [5, 6] asserted that the source of the HIS is lipid droplets localized within the pituicytes of the posterior lobe.

In their Introduction [1], Kucharczyk et al. lead the reader to believe that they were the first, in a paper published in 1986 [7], to report the relationship between this signal and the function of the posterior lobe. In fact, the paper had no description of this relationship. In this experimental study [1], they argue their thesis. However, we have found many misrepresentations, which should be criticized from a scientific point of view.

First, the most serious invention is found in two electron micrographs (Fig. 3 in reference 1) of feline posterior lobes. These photographs are negative electron micrographs. In all scientific research involving electron microscopy, negative micrographs are never used. Yet, Kucharczyk et al. have interpreted white particles in these micrographs as the lipid droplets. On conventional positive electron micrographs, these white particles would not show up as white; they would be electron-dense particles instead, which probably would indicate the presence of lysosomes, not lipid droplets [8]. Additionally, lipids never are washed out during osmium fixation. The thesis of Kucharczyk et al. is based mainly on the number of lipid droplets seen in these falsely represented electron micrographs.

Second, they stained the specimens of the dog pituitary gland with oil red O to show lipid droplets. When oil red O is used, water should be used to wash out excessive dye; the technique involves overstaining, followed by carefully monitored destaining, called the differentiation of staining. We think that the dog specimen (Fig. 1B in reference 1) is one that either has not been differentiated or has undergone insufficient differentiation.

Third, lipid droplets are abundant in rat pituicytes [9], but pituicytes of other animals have no or few lipid droplets (e.g., the rabbit posterior lobe has none [10]). We suspect that the reason for the authors' inventions is their inability to identify the lipid droplets in the cat and dog posterior lobes distinctly enough to show the changes in the numbers of these droplets.

Fourth, although Kucharczyk et al. did not determine the number of NSGs containing ADH in their experiment, they stated in the Abstract that they had seen an increase in these granules. They also speculated that the source of the HIS might be the NSGs, although they did not perform any experiments involving NSGs. In addition, not even the Discussion has a description of the NSGs. In an earlier paper [6], they stated that our hypothesis about NSGs was premature. In our opinion, it is incredible that they accepted our hypothesis without performing any of their own scientific observations to substantiate it.

Fifth, the central and peripheral effects of epinephrine on ADH vary according to dose, anesthesia, and so on. Thus, the effects are

controversial [11]. It is the same with isoproterenol. One of the problems in the experiment of Kucharczyk et al. is the use of these drugs.

Sixth, they observed changes in the volume of the HIS after administration of drugs. We think that it would be better to examine changes in signal intensity because the signal intensity of the posterior lobe, not the volume, reflects the number of lipid droplets.

Finally, we do not think that lipid droplets are the source of the HIS of the posterior lobe. The lipid droplets in the pituicytes consist of phospholipid [9], which does not have a visible signal in proton MR imaging [12]. Lipid-containing triglycerides in fat do have a hyperintense signal on T1-weighted images [12], which must show chemical-shift misregistration [13]. However, this phenomenon is never seen with the HIS of the posterior lobe [14].

In our experimental study with rabbits [15], the HIS disappeared after the rabbits were given hypertonic saline for 2 weeks, which is known to cause the loss of NSGs in the posterior lobe [16]. Thus, we suggest that the NSGs are the source of the HIS of the posterior lobes on T1-weighted MR images.

Drayer [17] has stated this about the controversy associated with our findings: "These disagreements are extremely healthy and should provide a fertile ground for exciting and innovative experimentation." We regret that the dishonesty and mispresentation in the paper by Kucharczyk et al. destroyed such an opportunity for healthy controversy.

Ichiro Fujisawa
Reinin Asato
Kyoto University, School of Medicine
Kyoto, 606 Japan
Mitsuhiro Kawata
Kyoto Perfectural University of Medicine
Kyoto, 602 Japan

REFERENCES

1. Kucharczyk J, Kucharczyk W, Berry I, et al. Histochemical characterization and functional significance of the hyperintense signal on MR images of the posterior pituitary. *AJNR* **1988**;9:1079–1083
2. Fujisawa I, Asato R. MR imaging findings in the posterior pituitary gland (letter to the editor). *Radiology* **1988**;168:282
3. Colombo N, Berry I, Kucharczyk J, Kucharczyk W. [Response to letter to the editor by Drs. Fujisawa and Asato]. *Radiology* **1988**;168:282–283
4. Fujisawa I, Nishimura K, Asato R, et al. Posterior lobe of the pituitary in diabetes insipidus: MR findings. *J Comput Assist Tomogr* **1987**;11: 221–225
5. Colombo N, Berry I, Kucharczyk J, et al. Posterior pituitary gland: appearance on MR images in normal and pathologic states. *Radiology* **1987**; 165:481–485
6. Kelly WM, Kucharczyk W, Kucharczyk J, et al. Posterior pituitary ectopia: an MR feature of pituitary dwarfism. *AJNR* **1988**;9:453–460
7. Kucharczyk W, Davis DO, Kelly WM, et al. Pituitary adenoma: high-resolution MR imaging at 1.5 T. *Radiology* **1986**;161:761–765
8. Bloom W, Fawcett DW, eds. *A textbook of histology*, 10th ed. Philadelphia: Saunders, **1985**
9. Gerch I. The structure and function of the parenchymatous glandular cells in the neurohypophysis of the rat. *Am J Anat* **1939**;64:407–443
10. Fujita H, Hartman JF. Electron microscopy of neurohypophysis in normal adrenalin-treated and pilocarpine-treated rabbits. *Z Zellforsch* **1961**;54: 734–763
11. Reid IA, Schwartz J, Ben L. Maselli J, Keil LC. Interactions between vasopressin and the renin-angiotensin system. *Prog Brain Res* **1983**; 60:475–491
12. Yoshikawa K, Ohsaka A. Nuclear magnetic resonance of rat skin. *Physiol Chem Phys* **1979**;11:185–188
13. Soila KP, Viamonte M Jr, Starewicz PM. Chemical misregistration effect in magnetic resonance imaging. *Radiology* **1984**;153:819–820
14. Fujisawa I, Asato R, Nishimura K, et al. Anterior and posterior lobes of the pituitary gland: assessment of 1.5 T MR imaging. *J Comput Assist Tomogr* **1987**;11:214–220
15. Fujisawa I, Asato R, Kawata M, et al. Hyperintense signal of the posterior pituitary on T1-weighted MR images: an experimental study. *J Comput Assist Tomogr* **1989**;13:371–377
16. Sloper JC. The experimental and cytopathological investigation of neurosecretion in the hypothalamus and pituitary. In: Harris GW, Donovan BT, eds. *The pituitary gland*, vol. 3. London: Butterworths, **1966**:131–239
17. Drayer BP. Balance between creativity and anatomic correlation in image interpretation. *Radiology* **1988**;168:214

Reply

Rather than responding in kind to the rhetoric contained in the letter by Fujisawa et al., we would like to address each of their substantive points in relation to our article, "Histochemical Characterization and Functional Significance of the Hyperintense Signal on MR Images of the Posterior Pituitary" [1].

Fujisawa et al. apparently think that our article failed to acknowledge their original proposal about the possible functional relevance of the pituitary hyperintensity. In fact, in the first two paragraphs of the Introduction, we cite a total of five references, two of which are articles by Fujisawa et al. We never have disputed the fact that Fujisawa et al. produced the first full paper suggesting that the pituitary "bright spot" might be related to hypothalamic-neurohypophyseal secretion of antidiuretic hormone (ADH).

To put this issue in historical perspective, it should be pointed out that an earlier article by Mark et al. [2] had assigned the pituitary hyperintensity to a "sellar fat pad." The original purpose of our investigation at UCSF was to establish if the hyperintensity was intra- or extraglandular. Once we were convinced, on anatomic grounds, that the high-intensity signal originated in the posterior lobe, we began to examine its chemical source and functional significance. Our first report that the posterior pituitary hyperintensity might reflect an intact hypothalamic-neurohypophyseal secretory system was made at the Western Neuroradiological Society meeting in October 1986, approximately 6 months before Fujisawa et al. [3] first dealt with this issue. Our next communication was in May 1987 at the meeting of the American Society of Neuroradiology, for which abstracts were submitted on January 16, 1987. Our major thesis had been that the hyperintensity is derived from some sort of lipid-based signal. Fujisawa et al., on the other hand, asserted that the high-intensity signal is due to ADH-containing neurosecretory granules in the posterior lobe. Inasmuch as the pituicytes in the posterior lobe contain variable amounts of lipid, depending on the level of ADH neurosecretory activity, it is quite conceivable that our theory and that put forward by Fujisawa et al. are not necessarily mutually exclusive.

Fujisawa et al. are also critical of the electron micrographs published in our article [1] because the micrographs are negatives. Although electron micrographs usually are published as positives, this in no way invalidates our interpretation about pituitary lipid droplets. The lipid droplets can be distinguished from lysosomes in both negatives and positives on the basis of their uniform density and morphology [4]. The electron micrographs were prepared from pituitary tissues from cats and rats that were processed according to standard published techniques [5]. Similarly, the oil red O stain for lipids was used on dog pituitary tissue that had been prepared and washed by using standard histologic methods.

In terms of quantifying the ultrastructural changes between the normally hydrated and dehydrated neurohypophysis (Figs. 3A and 3B, respectively, in reference 1), we stated in the Results section that the major difference observed was "a large increase in the number and size of lipid droplets interspersed throughout the pituicyte

cytoplasm in the dehydrated animals." We also saw a significant increase in neurosecretory granules in dehydration-stimulated cats. Fujisawa et al. interpret these observations to mean that we now have accepted their hypothesis that the pituitary hyperintensity is due to ADH in neurosecretory granules. In actual fact, on anatomic grounds again, the findings could be related to either lipid or ADH, or even some other posterior-lobe material signal. As stated earlier, no convincing causal relationship has emerged on this issue.

We agree that the effects of epinephrine and isoproterenol are complex. Our only objective in using these drugs was to induce changes in ADH secretion that were associated with acutely increased or decreased mean arterial blood pressure, an association that is now well established in the literature. Changes in pituitary signal intensity associated with epinephrine- and isoproterenol-induced changes in blood pressure are nonspecific. This could mean that the hyperintensity is the result of increased ADH, lipid droplets, or both. Again, more definitive experiments are required to answer this question.

As additional support for their argument against a lipid-related hyperintensity, Fujisawa et al. state that the lipid droplets in the pituicytes consist of phospholipids, which they claim do "not have a visible signal in proton MR imaging." We disagree with this statement. Phospholipids can contribute significantly to MR signal intensity, providing that they are mobile and not membrane bound. Cytoplasmic mobility appears to be a hallmark characteristic of pituicyte lipid droplets, which migrate in association with terminal axons containing neurosecretory granules [6].

Fujisawa et al. were the first to report that the pituitary high-intensity signal does not show a chemical shift, and they have argued that this excludes lipid as a possible source of this signal. We agree with their finding, but rather than summarily dismiss lipid, we have explored an alternative explanation, namely, that some lipid resonances (e.g., unsaturated groups) may overlap with the water peak and hence would not shift chemically with respect to water protons. Such lipids do exist, but they are almost always associated with and outnumbered by aliphatic groups, which, of course, do display a chemical shift. On this basis, we agree that the demonstration of a lack of a chemical shift by Fujisawa et al. is a strong argument against lipid protons being the source of the signal, unless a highly unsaturated fat exists in the posterior lobe. So far, we have been unable to show the presence of such a fat. On the other hand, if the pituitary hyperintensity is due to ADH/neurophysin in neurosecretory granules, as Fujisawa et al. propose, it would mean that these polypeptides behave differently from any other proteins in terms of their MR characteristics, in that they yield a hyperintense signal on both T1-weighted (short TR, short TE) and proton-density (long TR, short TE) images. Another potential problem for the hypothesis of Fujisawa et al. is that ADH apparently is found in low concentrations in the pituitary (nanogram/milligram of wet weight tissue in the rat), which may be too low to be detected with proton MR at 1.5–2 T. Furthermore, no one has yet described a plausible mechanism as to how a short-chain polypeptide can account for the observed MR signal.

In summary, the posterior lobe of the pituitary gland has MR signal characteristics that may be related to its neurosecretory and/or metabolic activity. The presence of lipid droplets in the pituicytes is an observation that is already well reported in the physiologic literature. Our studies, as well as those carried out previously by other research groups, have shown that these lipid droplets increase in response to stimuli that also increase synthesis of ADH and accumulation of neurosecretory granules in the posterior lobe. We previously had postulated that this lipid could account for the observed signal intensity, as it was present in relatively large amounts. However, although certain lipid proton resonances overlap with the water peak, we have not been able to identify them in the posterior lobe in sufficient quantity to account for the hyperintensity. On the basis of the currently available data, it is therefore unlikely that the MR signal characteristics of the neurohypophysis are related to the lipid droplets per se. Additional studies on the biochemical nature of this high-intensity signal are warranted, in particular, to identify the chemical source of the signal and to investigate the mechanism by which the material present in the posterior lobe either causes T1 shortening or has a short T1 relaxation time itself.

Finally, a comment about the tone of the letter from Dr. Fujisawa and colleagues might be appropriate. We have a high regard for the quality and originality of their work. Observations on the high-signal intensity of the posterior lobe of the pituitary gland are intriguing and challenging, in that they present an opportunity to correlate structure, signal intensity, and function in a clinical setting. It is unfortunate that Fujisawa et al. could not criticize our different views on this issue without resorting to phrases like "misrepresentation," "invention," and "dishonesty and misrepresentation." We regard the scientific literature as an arena for constructive and healthy interaction. Ultimately, the nature of the high-intensity signal will be delineated clearly. There will be no saints or villains, honest or dishonest men, but simply another scientific issue resolved.

David Norman
John Kucharczyk
Walter Kucharczyk
Hans Newton
University of California, San Francisco, Medical Center
San Francisco, CA 94143

REFERENCES

1. Kucharczyk J, Kucharczyk W, Berry I, et al. Histochemical characterization and functional significance of the hyperintense signal on MR images of the posterior pituitary. *AJNR* **1988**;9:1079–1083
2. Mark L, Pech P, Dnaiels D, Charles C, Williams A, Haughton V. The pituitary fossa: a correlative anatomic and MR study. *Radiology* **1984**;153: 453–457
3. Fujisawa I, Nishimura K, Asato R, et al. Posterior lobe of the pituitary in diabetes insipidus: MR findings. *J Comput Assist Tomogr* **1987**;11: 221–225
4. Takei Y, Seyama S, Peal GS, et al. Ultrastructural study of the human neurohypophysis. II: Cellular elements of the neural parenchyma, the pituicytes. *Cell Tissue Res* **1980**;205:273–287
5. Tweedle CD, Hatton GI. Ultrastructural changes in rat hypothalamic neurosecretory cells and their associated glia during minimal dehydration and rehydration. *Cell Tissue Res* **1977**;181:59–92
6. Tweedle CD, Hatton GI. Evidence for dynamic interactions between pituicytes and neurosecretory axons in the rat. *Neuroscience* **1980**;5:661–667