Robert A. Zimmerman, M.D.
Larissa T. Bilaniuk, M.D.

Age-Related Incidence of Pineal Calcification Detected by Computed Tomography[1]

The age-related incidence of detectable pineal calcification in 725 patients (age range, newborn-20 yrs.) suggests that there is a relationship between calcification and the hormonal role played by the pineal gland in the regulation of sexual development. Pineal calcification (demonstrated by computed tomography [CT] on 8-mm-thick sections) in patients less than 6 years old should be looked upon with suspicion, and follow-up CT should be considered to exclude the possible development of a pineal neoplasm.

Index terms: Head, computed tomography, 1[0].1211 • Pineal gland • (Skull, pinealoma, 1[0].3621)

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THE purpose of this study was to determine, using computed tomography (CT), the normal age-related incidence of pineal calcification in the first two decades of life. This study was prompted by a review of the CT findings in 32 pineal, parapineal, and histologically related tumors (1). In reviewing the CT literature on pineal tumors, it became apparent that specific information regarding the age at which normal pineal calcification can first be detected by CT was not available. That this age-related incidence is not the same for CT and skull radiography is obvious when one considers the tenfold or better sensitivity of CT in the detection of calcification (2).

Information exists on the incidence of pineal calcification as detected by skull radiography for different populations of the world (3-7). Pineal calcification can also be demonstrated by microradiography of pineal specimens that have been removed at autopsy (8-9), by measurement of pineal weight before and after decalcification (10), and by x-ray defraction studies (11, 12). While the incidence of pineal calcification is shown by those methods, the significance of this "physiologic" calcification is less well understood. Recent developments in the field of pineal neuroendocrinologic function indicate an apparent age-related coincidence between the occurrence of calcification and the hormonal regulation of sexual development.

METHODS

The CT examinations of 725 consecutive new patients (age range, newborn-20 yrs.) were reviewed for the presence of pineal calcification. All patients with pineal, parapineal, or histologically related tumors were excluded, as were patients with symptoms referable to the pineal and parapineal structures. The majority of patients included in the study had a history of seizures or minor head injury. All of the studies were interpreted as normal. Patients with a history of seizures and normal CT examinations did not usually undergo follow-up CT examination. Most patients with head injuries underwent follow-up CT 3 to 6 months after the trauma. The youngest patient with normal pineal calcification (age $6\frac{1}{2}$ yrs.) had a follow-up CT examination 2 years after a minor head injury.

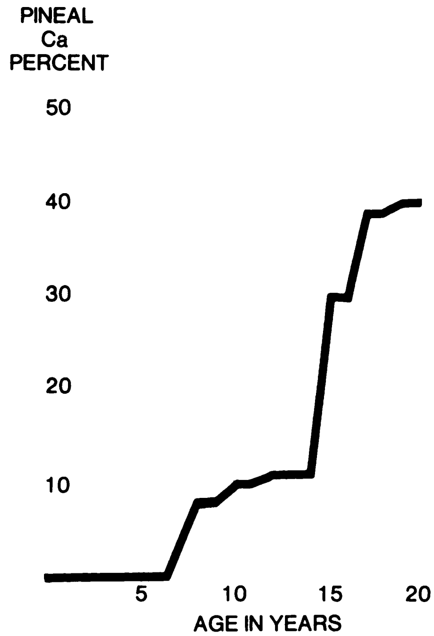
The CT examinations were performed with either an EMI 1005 head scanner (160 × 160 matrix, 8-mm-thick slices) or an EMI 5005 body scanner (160 × 160 or 320 × 320 matrix, 8-mm-thick slices). The sections were contiguous in all cases. Nonenhanced scans were evaluated for the presence of pineal calcification.

RESULTS

Of the 725 patients in this study, 648 had no evidence of pineal

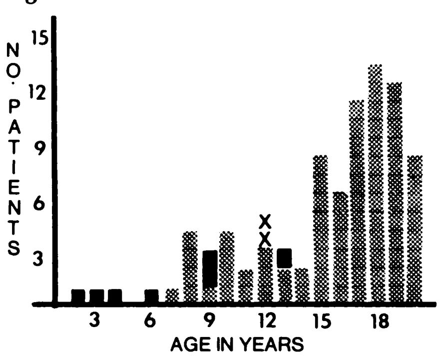
[1] From the Neuroradiology Section, Radiology Department, Hospital of the University of Pennsylvania, Philadelphia, PA. Presented at the Sixty-sixth Scientific Assembly and Annual Meeting of the Radiological Society of North America, Dallas, TX, Nov. 16-21, 1980. Received April 1, 1981; accepted and revision requested July 7; revision received Oct. 20. cd

Figure 1



Age-related incidence of pineal calcification as detected on 8-mm-thick sections in 725 patients who ranged in age from newborn to 20 years.

Figure 2



Age distribution of normal and pathologic pineal calcification in 87 patients. Normal pineal calcification = hatch mark bars; normal pineal calcification surrounded by pineal tumor (noncalcific tumor matrix) = X; abnormal pineal calcification = black bars. Note: A $6\frac{1}{2}$-year-old patient with normal pineal calcification is shown as age 7.

calcification on CT, and 77 did. The percentage of CT-detectable pineal calcification according to the patient's age is given in Figure 1. During the period that the 725 normal CT studies were collected, pineal calcification and primary pineal tumors were diagnosed by CT in 10 patients (birth–20 yrs.). Histologic examination showed these tumors to be pineoblastoma (3 patients), pineocytoma (2 patients), embryonal cell carcinoma (2 patients), embryonal cell carcinoma with entodermal sinus changes (1 patient), teratoma (1 patient), and germinoma (1 patient). If one applies the pineal calcification size criteria used for skull radiographs (abnormal = >1 cm in any dimension), the radiographic findings in these patients were: abnormally large (3 patients), abnormal in configuration (appearance of 2 teeth) and by early appearance (age 4 yrs.) (1 patient), and normal (6 patients). Applying the same size criteria to CT, the pineal calcification in the tumor cases was abnormal in 4, just below top normal in 2, and normal in 4. If the criteria of abnormal size and distribution of calcification are used, 8 out of 10 tumors showed pathologic pineal calcification. A comparison of the age distribution of normal and pathologic pineal calcification is given in Figure 2.

DISCUSSION

The pineal body was known to Galen in the third century, and described by Descartes in the 1600s as the seat of the soul (13). Its functional significance was first suspected in 1898, when Huebner described a case of a pineal tumor that was associated with precocious puberty (14). It was not long after Roentgen's discovery of the x ray in 1896 that Schiller (1918) first described pineal calcification on skull radiographs (15). During the past six decades, the identification of pineal calcification has been of interest to the radiologist because pineal displacement has indicated intracranial space-occupying processes, pineal enlargement has indicated pineal tumors, and the incidence of pineal calcification has indicated some genetic factors.

The incidence of radiographic pineal calcification that has been reported in the literature has varied depending on the age of the population examined, the quality of the radiographic examination, and the genetic makeup of the population. A further factor in the differences between reported incidences of pineal calcification in earlier studies relates to the inclusion of calcification of structures other than the pineal body (habenula, choroid plexus, and tentorium). Vastine and Kinney reported an incidence of 47.9% (16) in 1927, and Dyke reported an incidence of 51% (17) in 1930. In both of these series, the populations were composed mostly of older adults. In the more recent series of Adeloye and Felson (5), the overall incidence was 12.2%. Adeloye and Felson differentiated between the incidence in American blacks (9.7%) and American whites (16%). Series from other countries have varied from 5% for Nigerians (18), to 9.9% for the Japanese (4), to 15% for Fijians (7), to 19 to 24% for Indians (6).

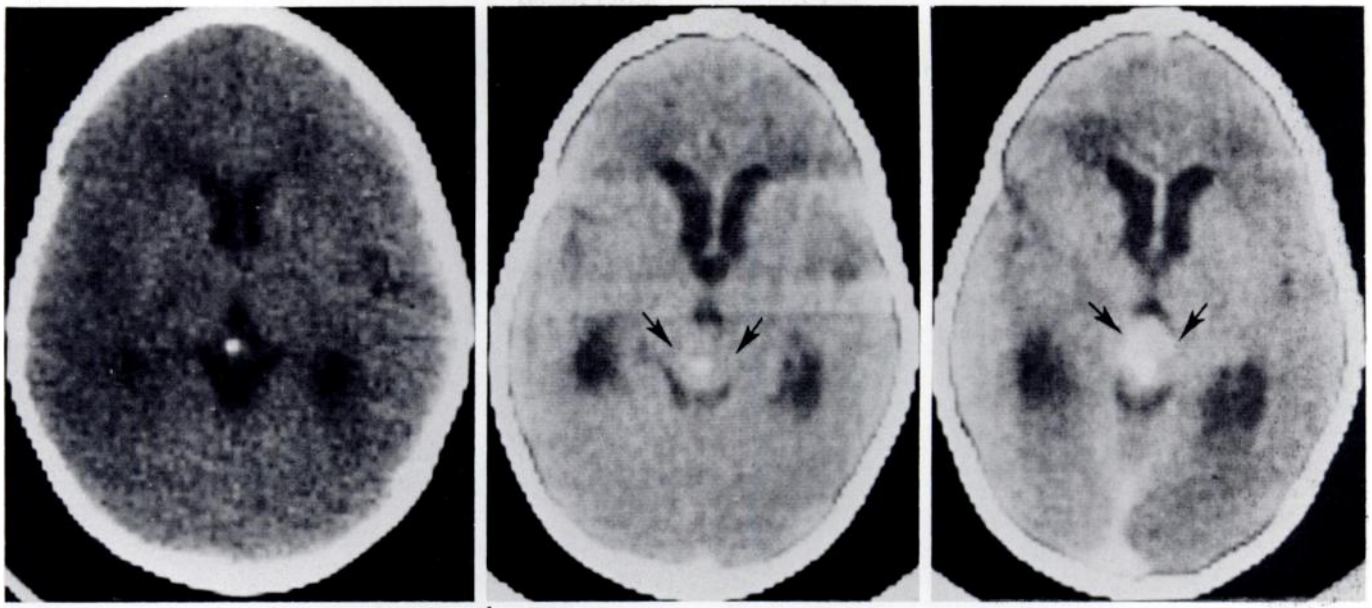
Very similar incidences of calcification per decade of life were found by Adeloye (5) in the American population and by Bhatti (6) in the Pakistani population. The incidence was 0% for the first decade of life in both series, 2.3% for the second decade in Americans and 1.5% in Pakistanis, and 10.5% for the third decade in both populations. In the American series, there was a slow progressive rise in the incidence of pineal calcification to a level of 30% by the seventh decade, while in the Pakistani series, a 30% incidence was reached in the fourth decade and persisted at that level thereafter.

Is calcification of the pineal gland acceptable as a normal radiographic finding in persons less than 10 years old? Schey (19) states that "physiologic" calcification is never seen in persons less than 6 years old, while Wilich *et al.* (20) give the incidence of pineal calcification in children as 0.83%, and Peterson and Kieffer (21) accept a 5.1% incidence. In the evaluation of a child under age 10 with pineal calcification on skull radiographs, age is not the only important factor. Also significant are the symptomatology, the position of the pineal gland (*e.g.*, whether it is inferiorly displaced by hydrocephalus), and the nature (22) and the size of the calcification (23). The normal pineal gland is 5 to 9 mm in length, 3 to 6 mm in width, and 3 to 5 mm in height. It has been accepted that a calcification wider and longer than 1 cm is abnormal (23).

The tenfold greater sensitivity of CT in the detection of calcification over that achieved with skull radiography (2) indicates that pineal calcification should be more readily detected by CT. Thus, smaller amounts of calcification in younger patients may be expected to be recognized with CT. Harwood-Nash and Fitz (23) state that calcification in the pineal glands of children as young as 2 years of age has been demonstrated by CT. The implication is that this is normal, and Harwood-Nash and Fitz show "normal" pineal calcification in a 4-year-old child.

Norman *et al.* (2) deal with the effi-

Figure 3



a. b. c.

Pineoblastoma.

a. This 3-year-old girl was examined with CT as part of a routine follow-up for treatment of a radiation-induced undifferentiated sarcoma of the face (radiation given for bilateral congenital retinoblastomas at age 6 months). Pineal calcification without evidence of a soft-tissue mass is present.

b. CT examination 16 months later shows hydrocephalus due to an isodense pineal soft-tissue mass (arrows) that surrounds the pineal calcification.

c. CT examination following injection of contrast material shows enhancement of the mass (arrows).

cacy of CT in detecting pineal calcification compared with skull radiography. CT detectability of pineal calcification varies with the thickness of the section (thinner sections are more sensitive because of less value averaging), the density of the gland's calcification, and the volume of the gland that is calcified (2). Smaller calcifications are more detectable if denser, and less dense calcifications are more detectable if larger. With 8-mm-thick sections, CT is 8 times more sensitive than skull radiographs in detecting calcifications that are 3 mm in diameter, and 22 times more sensitive in detecting calcifications that are 10 mm in diameter (2).

In our 10 patients with primary pineal tumors, CT was positive relative to the size of the calcification or its distribution in 8 cases, whereas the skull radiographs were positive in only 4. CT has the advantage of demonstrating not only the calcification but also the surrounding soft-tissue components and the effect of the tumor on the ventricular system and cisternal spaces. When the 1-cm size criterion is applied to both the calcification and the soft tissues, 8 cases were abnormal initially. The 2 cases that were initially normal had tumors that subsequently grew and were abnormal at the time of diagnosis.

In the 725 normal patients reviewed in this series, the youngest patient with a normally calcified pineal body was $6\frac{1}{2}$ years old (Figs. 1 and 2). Calcification was found in from 8 to 11% of the population between ages 8 and 14 years, and the incidence rose markedly at age 15 to 30%, and then rose even further to 39 to 40% for the 17th to 20th year (Fig. 1). The presence of a small pineal calcification in patients who are at least $6\frac{1}{2}$ years of age, in and of itself, is not evidence of a pineal neoplasm. There is no guarantee that the pineal gland that harbors such a calcification will not subsequently be associated with the development of a pineal neoplasm. However, in Americans, pineal calcification in persons less than 6 years old must be looked on with increased suspicion (Figs. 2 and 3).

Microradiographic studies of pineal glands that have been removed at autopsy reveal a higher incidence of calcification than that detected by CT (8, 9). Forty-three per cent of Ugandans had significant deposits of calcification by age 10, and 68% had significant calcification by the fourth decade (8). Measurement of the pineal weight before and after decalcification demonstrates a small but significant incidence of calcification during the first decade of life (10). This method also shows that the weight of calcium within the pineal gland is fairly constant from the 30s on into old age. The only decrease in weight of calcium has been after menopause in women. Recent studies of the ultrastructure of the pineal calcification (12) indicate indirectly that ultrasmall calcific crystals are probably present in all pineal glands, even though they are undetectable by microradiography. What then is the significance of the calcification? Chemical analysis of the calcification indicates that it consists of hydroxyapatite and calcium carbonate apatite crystal (11, 12). The calcification, when grossly visible in the pineal gland, has a polycyclical appearance with a diameter of 0.5 mm (12). The calcification can be subdivided into nodules measuring 30 to 50 μm; these nodules can be further subdivided into particles measuring less than 0.1 μm. It is the extremely small particle that is most likely to be present in the radiographically noncalcified pineal gland (12). Levels of trace elements, including Zn, Fe, Mn, and Cu, have been found to be very high in the human pineal body. These levels are high in comparison with the levels in other structures in which calcium apatite crystals are basic, such as bone and teeth. The level of magnesium is also high in the pineal gland.

Calcification occurs in the presence of an organic matrix that is located both intracellularly and extracellularly within the pineal parenchyma, and in the connective tissue septa that support the gland (11). Large concentrations of hydroxyproline, indicating the presence of collagen, which is a well-known matrix for calcification, are present in the pineal body (12). Electron microscopy has raised the question of whether mucopolysaccharides are another source of the calcification matrix (12). Microradiographic studies indicate that radiographically visible calcification is most frequent at the base of the gland and in the connective tissue septa (11). That the calcification is not part of a degenerative process is indicated by the histologic findings of only mild fibrosis and gliosis in the calcified pineal body of older patients.

What occurs in the pineal gland that causes the calcification to become progressively more aggregated, and therefore more radiographically detectable during the first two decades of life? This question is thus far unanswered. An understanding of the neuroendocrinologic function of the pineal gland may provide an answer in the near future. Kitay (14) observed that one third of young male patients with pineal tumors had precocious puberty. Experimental evidence now exists both in animal and man that the pineal body plays a major role in the regulation of the onset of puberty (24, 25). The pineal gland contains a number of hormones, only some of which have been identified. Melatonin is synthesized in the body only within the pineal gland (24). Tryptophan is converted to serotonin (found within the pineal parenchymal cells), which is then converted to melatonin through the enzymatic action of 5-hydroxyindole-o-methyltransferase (found only in the pineal gland). Released melatonin directly affects the hypothalamus, midbrain, and pituitary function, so that the production of luteinizing hormone and follicle stimulating hormone is depressed (24). Measurements of the blood melatonin level in prepubertal and pubertal boys show a significant drop in the level of blood melatonin immediately preceding the rise in gonadotropins and testosterone that accompanies puberty and precedes its physical signs (25). A further indication of hormonal calcification interrelationship is found in human females, where the weight of pineal calcification decreases after menopause (age 60 and up) (10).

The incidence of pineal calcification demonstrated by less sensitive means such as skull radiography, more sensitive means such as CT, and still more sensitive means such as the microradiography shows a correlation between the detectability of pineal calcification and the prepubertal, pubertal, and postpubertal periods. The interrelationship between the aggregating pineal calcification and hormonal function has not been proven, nor is it certain that, if a hormonal relationship is proven, the hormone will be melatonin (24).

Robert A. Zimmerman, M.D.
Neuroradiology Section
Radiology Department
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104

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