Idiopathic scoliosis and pineal lesions in Australian children

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ABSTRACT

Purpose. To determine whether treatment of pineal lesions in children is associated with development of idiopathic scoliosis.
Methods. 38 boys and 10 girls with pineal lesions were identified. Their mean age at presentation was 10 years. The pineal pathology varied from cysts and epidermoid to teratoma, germinoma, pineocytoma, and glioblastoma. Treatment ranged from biopsy/extirpation to radiotherapy.
Results. 12 patients died. No scoliosis was found in any females or any of the deceased. Two boys had scoliosis: one had a 12-degree right upper thoracic curve with 32-degree kyphosis and the other had a 60-degree right thoracolumbar idiopathic curve, requiring a 2-stage arthrodesis.
Conclusion. Pineal ablation is not related to the development of idiopathic scoliosis in humans.

Key words: *pineal gland; scoliosis*

INTRODUCTION

The relationship between pinealectomy, melatonin levels, and development of scoliosis is controversial and the results from animal studies are contradictory. Experimental pinealectomy in 3-day-old white leghorn chickens of both sexes leads to the development of thoracic scoliosis,[1,2] whereas a sham procedure does not.[3,4] The critical step is to remove the entire pineal gland and/or stalk.[5,6] 50 to 100% of pinealectomised chickens develop scoliosis.[1,3,7–10] Although the incidence of scoliosis is dependent on age at pinealectomy,[11] the prevalence of scoliosis in chickens pinealectomised between 2 and 18 days after hatching is not significantly different.[4] The induced scoliosis was similar to human idiopathic scoliosis.[2] Angular thoracic scoliosis has been reported in some pinealectomised chickens as well as controls.[10,12] Intra-muscular auto-transplantation of the pineal gland into pinealectomised chickens prevented the scoliosis developing in 90% of them,[2] but this was subsequently refuted.[13,14]

Melatonin (N-acetyl-5-methoxytryptamine) is the only hormone secreted by the poultry pineal gland.[15]

Table
Patient characteristics and outcomes

Patient No.	Sex/age (years)	Diagnosis	Surgery	Radio-therapy	Chemo-therapy	Died	Lesion site	Scoliosis
1	M/11	Central nervous system germinoma	Yes	Yes	Yes	No	Pineal	No
2	M/12	Intracranial germ cell	Yes	No	Yes	No	Pineal	No
3	F/9	Intracranial germ cell	No	Yes	No	Yes	Pineal	No
4	M/14	Intracranial germ cell	Yes	Yes	Yes	No	Pineal	No
5	M/4	Intracranial germ cell	No	No	Yes	No	Pineal	No
6	M/16	Intracranial germ cell	Yes	Yes	Yes	No	Pineal & suprasellar	No
7	M/13	Intracranial germ cell	Yes	No	Yes	No	Pineal & suprasellar	No
8	M/15	Intracranial germ cell	Yes	Yes	No	No	Pineal	No
9	F/13	Intracranial germ cell	Yes	No	Yes	Yes	Pineal	No
10	M/9	Intracranial germ cell	Yes	Yes	Yes	No	Pineal & suprasellar	No
11	M/11	Intracranial germ cell	Yes	No	Yes	No	Pineal	No
12	M/14	Intracranial germ cell	Yes	No	Yes	No	Pineal	No
13	M/15	Intracranial germ cell	Yes	No	Yes	No	Pineal	No
14	M/13	Intracranial germ cell	Yes	Yes	Yes	Yes	Pineal	No
15	M/9	Intracranial germ cell	Yes	Yes	Yes	Yes	Pineal	No
16	M/14	Intracranial germ cell	Yes	Yes	No	No	Pineal & suprasellar	No
17	M/14	Intracranial germ cell	Yes	Yes	Yes	No	Pineal	No
18	F/2	Intracranial germ cell	No	No	No	Yes	Pineal	No
19	M/8	Intracranial germ cell	Yes	Yes	Yes	No	Pineal	No
20	M/9	Intracranial germ cell	No	Yes	Yes	No	Pineal	No
21	M/13	Intracranial germ cell	Yes	Yes	Yes	No	Pineal	No
22	M/10	Intracranial germ cell	Yes	Yes	Yes	No	Pineal	No
23	F/3	Pinealoblastoma	Yes	Yes	Yes	Yes	Pineal	No
24	M/14	Pinealoblastoma	Yes	Yes	Yes	No	Pineal	No
25	M/3	Pinealoblastoma	Yes	No	Yes	Yes	Pineal	No
26	M/5	Pinealoblastoma	Yes	Yes	Yes	No	Pineal	No
27	M/11	Pineal germinoma	Yes	No	No	No	Pineal	No
28	M/5	Germ cell tumour	Yes	No	Yes	No	Pineal	T5–T8, right, 12°
29	M/12	Pineal cyst	Yes	No	No	No	Pineal	T6–L1, right, 60°
30	F/14	Calcified pineal tumour	Yes	No	No	No	Pineal	No
31	M/18	Pinealoma	No	No	No	No	Pineal	No
32	M/4	Leptomeningeal dis	Yes	Yes	No	No	Pineal	No
33	M/6	Pinealoma	No	No	No	No	Pineal	No
34	M/9	Pineal teratoma	No	No	No	Yes	Pineal	No
35	F/17	Pineoblastoma	Yes	No	No	Yes	Pineal	No
36	F/11	Pineal region astrocytoma	Yes	No	Yes	No	Pineal	No
37	M/5	Pineal glioblastoma	Yes	No	Yes	Yes	Pineal	No
38	M/13	Pinealoma	Yes	Yes	Yes	Yes	Pineal	No
39	M/5	Pineal teratoma malignant	Yes	Yes	Yes	No	Pineal	No
40	M/1	Glioma pineal region	Yes	No	No	Yes	Pineal	No
41	M/12	Pineal germ cell malignant	Yes	No	Yes	No	Pineal	No
42	M/5	Pineal-hypothalamic germ cell tumour	Yes	Yes	Yes	No	Pineal	No
43	F/12	Pineal germinoma	Yes	Yes	Yes	No	Pineal	No
44	F/5	Pineocytoma	Yes	No	No	No	Pineal	No
45	F/13	Pineal region epidermoid	Yes	No	No	No	Pineal	No
46	M/12	Pineal region teratoma	Yes	No	No	No	Pineal	No
47	M/6	Pineal germinoma	No	No	No	No	Pineal	No
48	M/12	Pineal germinoma	No	No	No	No	Pineal	No

Pinealectomy on 3-day-old chickens was associated with reduced melatonin levels and elimination of the melatonin circadian rhythm.[16] Although a low serum melatonin level was reportedly associated with scoliosis in pinealectomised chickens,[16] others found it a poor indicator for scoliosis.[4,17] Induced melatonin suppression by constant light resulted in scoliosis in 15% of white leghorn chickens,[18] but it had no effect on Nihon chickens.[9] Intra-peritoneal injections of melatonin (2.5 mg/100 mg body weight)

into pinealectomised white leghorn chickens for 3 weeks prevented scoliosis in 80%,[16] but injections of melatonin (2.5 mg/1 kg body weight) had no effect on pinealectomised Mountain Hubbard chickens.[19] The latter dose was to restore melatonin levels to a physiological range. Daily intraperitoneal injections of 5-hydroxy-l-tryptophan (a precursor of both serotonin and melatonin) into white leghorn pinealectomised chickens retarded scoliosis development in 30% of all the chickens.[20]

Other animal pinealectomy models (e.g. hamsters) also result in scoliosis.[8] Scoliosis did not develop in pinealectomised quadrupedal rats but developed in all pinealectomised bipedal male Sprague-Dawley rats suggesting a postural mechanism.[21] Scoliosis did not develop in young pinealectomised rhesus monkeys after a mean follow-up of 28 (range, 10–41) months.[22]

Pineal tumours and related conditions in humans are rare.[23–26] Scoliosis following pineal ablation in children has not been reported.[27] A retrospective study of scoliosis in children with a variety of pineal lesions may be the closest human model to compare with experimental pinealectomy in animals. We aimed to determine if idiopathic scoliosis was associated with prior treatment for pineal lesions in children.

MATERIALS AND METHODS

Medical records of 48 Australian children (38 boys and 10 girls) aged one to 18 (mean, 10) years presenting with pineal lesions between 1990 and 2003 were retrospectively studied (Table). Ethics approval was granted from relevant committees of the hospitals. Inclusion criteria were: patients with any kind of pineal lesions and non-pineal tumours compressing the pineal gland. Exclusion criteria were: patients aged >18 years at diagnosis and lesions not directly involving the pineal gland. Lesions varied from germ cell tumour, germinoma, pineoblastoma, pinealoma and teratoma to a pineal cyst and an epidermoid cyst. Melatonin levels were not recorded.

Of 36 surviving patients, clinical examination was not performed for 18 who had recently taken chest radiographs or spine magnetic resonance images (MRIs); 18 others took the Adam's forward bend test. Spine radiographs were not taken for patients with a straight spine and no truncal rotation. Thoracic and lumbar spine rotation was measured using a scoliometer. Plain chest radiographs or spine MRIs were available for the 12 deceased patients (7 boys, 5 girls) shortly before their deaths.

RESULTS

The mean follow-up period was 80 (range, 7–150) months for surviving patients and 30 (range, 1–142) months for the deceased. 39 patients underwent pineal gland surgery (partial or total excisional biopsy). 22 and 30 patients underwent adjuvant radiotherapy and chemotherapy, respectively.

None of the deceased were noted to have idiopathic scoliosis on their final chest radiographs or spine MRIs. Among the 36 survivors, only 2 of the 31 boys were noted to have scoliosis. One with a germ cell tumour at the age of 5 years had a 12° upper right thoracic scoliosis and a 32° kyphosis 8 years later (Fig. 1). At the age of 14 years, the kyphosis did not progress, the scoliosis diminished, and the spine became nearly straight. The other presented at age 16 years with a 60° right thoracolumbar curve (Fig. 2) and underwent an excision of a pineal cyst. Four years later, he underwent a 2-stage anterior and posterior arthrodesis. One boy without scoliosis was noted to have precocious puberty.

DISCUSSION

Cross-sectional comparisons between animal and human studies may not be appropriate, particularly in regard to the relationship between pineal function, melatonin, and scoliosis. Pinealectomy-induced scoliosis in chickens has similarities to human idiopathic scoliosis. Chicken scoliosis is 3-dimensional and involves rotation of the thoracic spine, producing a rib hump.[28] Single and double curves occur in both chicken and human scoliosis. The vertebral bodies in chicken and human idiopathic thoracic scoliosis are laterally wedged at the apex of the curve.[10,29,30] The vertebral wedging may be due to anatomic changes in the vertebral growth plates.[1] Differential pressures on the quadrants of the vertebral growth plates can cause the anatomic changes.[31,32] Anatomic differences between human and chicken spines cloud the comparisons of scolioses.[3,28] With spinal growth, most lumbar and thoracic vertebrae of chickens fuse,[28] whilst human vertebrae do not fuse spontaneously. In chickens the thoracic spine is naturally lordotic, whilst in humans it is kyphotic. A relative overgrowth of the anterior elements of the human spine, resulting in thoracic lordosis, is important in the pathogenesis of the 3-dimensional deformity of thoracic scoliosis.[33] This theory has been supported by radiological and MRI studies of idiopathic scoliosis.[34,35] Chicken scoliosis has no predilection for gender or side, whereas human idiopathic scoliosis commonly occurs
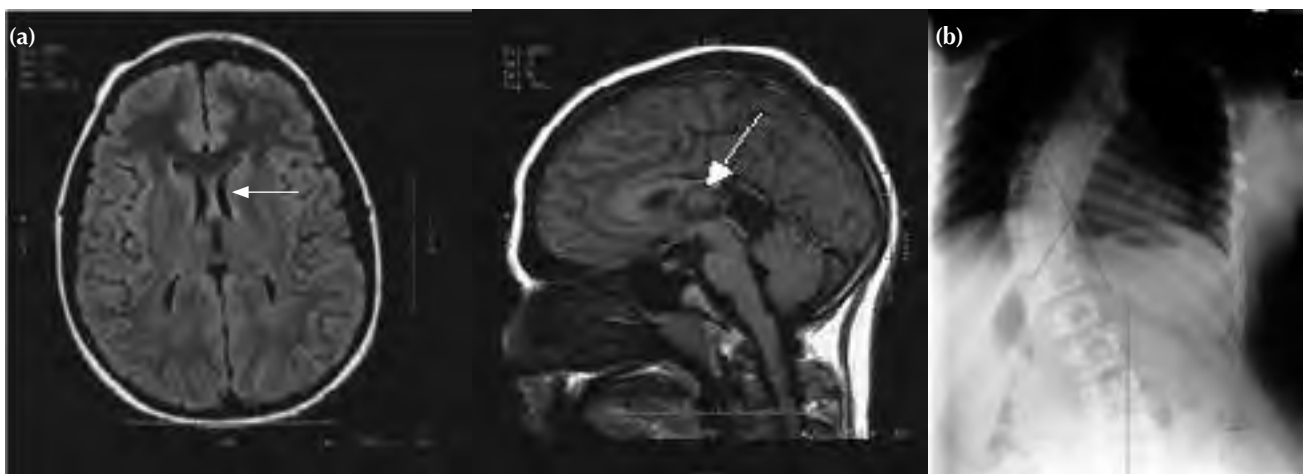
Figure 1   Radiographs of a 13-year-old boy showing a 12° upper right thoracic scoliosis and a 32° kyphosis.

on the right side of female thoracic spines. Scoliosis in pinealectomised chickens is only in the thoracic spine,[8] whereas human idiopathic scoliosis can also occur in the lumbar spine. The thoracolumbar junction was identified as the apex of the scoliotic curve in pinealectomised chickens.[36]

Although pinealectomy causes scoliosis in 50 to 100% of chickens, scoliosis also develops in 55 to

90% of highly inbred chickens originating from white leghorns.[37–39] 68% of the inbred roosters and 46% of the hens have scoliosis.[40] Three genes are responsible for such scoliosis.[41] Scoliosis has been experimentally enhanced in genetically engineered chickens by dietary means, including feeding aminonitriles or deprivation of trace nutrients such as copper, Vitamin B-6, or manganese.[42,43] Genetic studies of adolescent idiopathic scoliosis indicate that about 11% of first-degree relatives are affected, 2.4% for second-degree relatives, and 1.4% for third-degree relatives.[44–46] Monozygotic twins have a high concordance rate for idiopathic scoliosis (about 73%) compared to dizygotic twins.[47–49] Genetic linkages to chromosomes 6p, 10q, 18q,[50] 19p13,[51] 17p11,[52] and X[53] for adolescent idiopathic scoliosis have been reported.

The relevance of melatonin secretion in chickens to the development of experimental scoliosis is conflicting. Human adolescents[54,55] and juveniles[56] with progressive idiopathic scoliosis were reported to have reduced night-time serum levels of melatonin, although these findings have not been confirmed.[57–59] Methods for identifying melatonin secretion varied between studies and included night-time and day-time serum levels as well as 24-hour urinary excretion measurements. Because the ages of scoliotic subjects varied between reports, melatonin levels could influence pre-menarchal scoliotic development rather than in adolescence.[60] An abnormality of melatonin receptors was implicated in a study on Hereditary Lordoscoliotic Rabbits.[61] Polymorphism of melatonin 1A receptor on chromosome 4q was not linked with human idiopathic scoliosis.[62] Impaired melatonin signalling was linked with human idiopathic scoliosis but melatonin receptors were normal.[63]

Figure 2   **(a)** Magnetic resonance images of the brain of a 12-year-old boy showing a pineal cyst (arrows). **(b)** Radiograph showing right thoracic scoliosis at the age of 16 years.

Melatonin binds to platelet calmodulin with high affinity and acts as a calmodulin antagonist.[22] Platelet calmodulin is a critical mediator of cellular calcium function and a regulator of many enzymes. Elevated platelet calmodulin levels are found in children with progressive scoliosis.[64,65] Current controversy focuses on the lack of control data and the large variability of baseline platelet calmodulin levels in idiopathic scoliosis patients.[66]

For the purpose of clinical neuromotor assessment of children with idiopathic scoliosis, MRIs of the brain and spinal cord can help in the investigation of abnormalities of proprioception, postural equilibrium control, oculovestibular function, and vibratory sensation.[67–71] Younger children with progressive idiopathic scoliotic curves with and without neuromotor signs are more likely to have brain stem abnormalities such as Arnold-Chiari type-1 malformation, syringomyelia, or cerebellar tonsillar ectopia.[72–77] However, lesions involving the suprasellar region and pineal gland in juveniles have not been implicated in the development of idiopathic scoliosis.

Fundamental differences exist between methodologies of experimental chicken pinealectomy and this observational human study on the effects/ treatment of pineal lesions and the development of scoliosis. The chicken model was prospective and controlled with definitive proof of pinealectomy, but this study was not. The chicken pineal gland sits on the end of a long stalk in the frontal region of the brain, whereas in the human it is situated posterior to the pituitary gland. Pinealectomy was performed for chickens, whereas surgery, chemotherapy, radiotherapy, and/or ablation were performed for humans. These latter procedures may also affect the hypothalamus and suprasellar region.

The inability to confirm the timing and complete ablation of pineal function and any corresponding reduction of melatonin levels compromised the validity of our findings. Juvenile human serum melatonin levels appear to have a large standard deviation, severely limiting the usefulness of periodically recorded melatonin levels. The lack of complete radiological studies of the entire cohort and the lack of reliability of the scoliometer to detect scoliosis were other considerations. Nonetheless, our results demonstrated a trend.

The confirmation of scoliosis ultimately depends on radiological examination. According to the Scoliosis Research Society, the phenotypic definition of scoliosis is a lateral curvature of the spine of >10° with rotation of the vertebrae within the curve. The validity of our study depends on the reliability, sensitivity, and specificity of the Adam's forward bending test and the scoliometer to detect a rotational asymmetry indicative of scoliosis. The scoliometer is considered adequate, reliable, and reproducible in detecting rib hump rotation.[78–83] The correlation between asymmetry and scoliosis of >10° is high. In our study, patients with rib humps detected with a scoliometer had radiological studies to confirm the presence of scoliosis. It was unlikely that we missed a small scoliosis due to a false negative reading or misinterpretation of an Adam's forward bending test.

If the chicken model of experimental pinealectomy resulting in a 50 to 100% incidence of scoliosis was translated to human idiopathic scoliosis, then children with partial or complete pineal ablation should have had a substantially higher prevalence of scoliosis than 2 out of 48.

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