Atlanto-occipital Ligament Calcification: A Novel Sign in Nevoid Basal Cell Carcinoma Syndrome

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Abstract. *Background: The nevoid basal cell carcinoma syndrome (NBCCS), first described by Gorlin and Goltz in 1960, is a hereditary autosomal dominant disease with high penetrance and variable expressivity. Almost 70% of patients with NBCCS have some degree of craniofacial anomaly. Among these, the presence of ectopic calcification have been reported but Atlanto-occipital ligament calcification has never been described. Therefore this investigation was carried out to determine the prevalence of atlanto-occipital ligament calcification on lateral x-ray of NBCCS patients aiming to assess the effectiveness of this sign in NBCCS diagnosis. Patients and Methods: Lateral and frontal cephalometric radiographs of 18 patients (11 males and 7 females), aged 8-61 years, with the diagnosis of NBCCS were evaluated for the presence of intracranial calcifications (diaphragma sellae and falx cerebri) and or calcification of the atlanto-occipital ligament. Results: A total of 11 patients presented calcification of atlanto-occipital ligament to various degrees and in three cases this represented the only sign of ectopic calcification. When compared to the other two sites of ossification, atlanto-occipital ligament calcification had a similar prevalence. Conclusion: The calcification of the atlanto-occipital ligament should be considered in addition to the other major criteria for NBCCS diagnosis.*

The nevoid basal cell carcinoma syndrome (NBCCS) was first described by Gorlin and Goltz (1) in 1960 and often bears the former's name. It is a hereditary autosomal dominant disease with high penetrance and variable expressivity (2-4). About 40% of the cases represent new mutations (5, 6). The prevalence has been estimated as 1:56000 in the North West United Kingdom (7) and 1:164000 in Australia (8).

Clinical manifestations are extremely pleomorphic and include basal cell carcinomas (BCCs), odontogenic keratocysts (OKCs), palmar and plantar pits and lamellar calcifications of the *falx cerebri* (8) which are considered major diagnostic criteria (9). Other features include several radiologically evident manifestations (for review see 10, 11). Among these, the presence of ectopic calcifications have been reported for interclinoid ligament (bridging of the *sella turcica*), *tentorium cerebellum* and nuchal ligament together with the major sign of lamellar calcification of the *falx cerebri* (9, 10, 12). These calcifications are not specific for the syndrome, as they have been described in several conditions, but their presence in combination with other signs allow the diagnosis of NBCCS.

It has been claimed that in the absence of major features such as BCC, jaw cysts, or *falx* calcification, which are often not evident until the age of 10, other radiological manifestations of the disorder can permit early diagnosis of NBCCS in childhood (11, 13).

Atlanto-occipital ligament calcification (also called ponticulus posterior on the first cervical vertebra) has never been described as a sign of NBCCS, despite the considerable volume of literature from different countries about this syndrome. Like the others, this is a not specific calcification. However, it becomes visible early (14) and is easily detectable on lateral cephalometric x-ray. When present, the detection of atlanto-occipital ligament calcification could be of aid in the diagnosis of NBCCS.

Therefore, this investigation was carried out to determine the prevalence of atlanto-occipital ligament calcification on lateral x-rays of NBCCS patients and to compare its prevalence with calcifications of the *sella turcica* bridge and lamellar calcification of *falx cerebri*, aiming to assess the effectiveness of this sign in NBCCS diagnosis.

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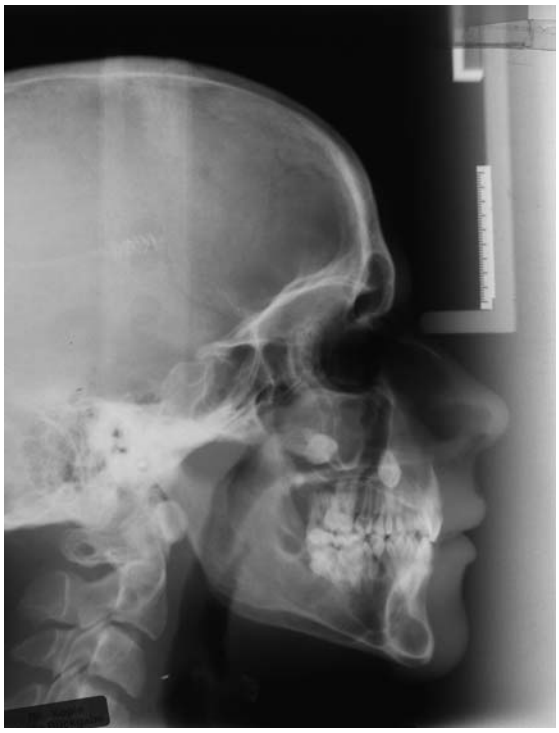

Figure 1. *Atlanto-occipital ligament calcification clearly detectable on lateral cephalometric x-ray.*

Patients and Methods

The study population consisted of 22 patients (14 males and 8 females), aged 8-61 years, with the diagnosis of NBCCS seen between 1990 and 2006. Clinical data for each patient (*e.g.* sex, age) were retrieved and only cases with histologically proven BCC or OKC with full case records with good quality lateral and frontal cephalometric radiographs (on the lateral x-ray at least the first three cervical vertebra should be detectable) were considered for this study.

The radiographs were evaluated on a masked, illuminated view-box in a room with reduced ambient light. Two authors (RL) and (EB) calibrated by scoring the first 10 radiographs together in order to establish an agreement. Then radiographs were interpreted and scored independently. In every case the following findings were recorded: (i) intracranial calcifications (*diaphragma sellae* and *falx cerebri*); (ii) calcification of the atlanto-occipital ligament .

A semi-quantitative assessment of the atlanto-occipital ligament calcification was performed assigning cases to one of the following three categories in view of the extent of the ossification. Cases were scored as: –, no calcification; +/–, incomplete calcification; and +, complete calcification. The other intracranial calcifications were reported as being present or absent.

The presence of calcifications and their score were tabulated and their prevalence compared. Data were analysed using GraphPad Prism software version 5.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com). Significant differences ($p<0.05$) between groups were determined using chi-square test.

Table I. *Prevalence of intracranial calcifications of the diaphragma sellae and falx cerebri and calcification of the atlanto-occipital ligament (ponticulus posterior or arcuate foramen).*

Case	Age (years)	Gender	Calcification		
			Atlanto-occipital ligament	Sella bridge	*Falx cerebri*
1	44	M	–	–	–
2	8	M	–	+	–
3	48	F	–	–	+
4	15	M	+	–	–
5	54	F	+	+	–
6	12	M	–	+	+
7	17	M	+	+	–
8	38	M	–	–	+
9	61	F	+/-	–	–
10	17	M	+	+	–
11	39	M	–	+	+
12	13	M	+/-	+	–
13	22	F	–	–	+
14	50	F	–	–	–
15	22	M	+	+	+
16	58	M	–	+	+
17	13	F	+	–	–
18	22	F	+	+	–
Total with calcification†			9	10	7
Without calcification			9	8	11

–, No calcification; +/–, incomplete; +, complete. †Chi-square test=1.038, *p*-value=0.5950.

Results

A total of 18 individuals (11 males and 7 females) fulfilled the inclusion criteria (Table I). Three patients were excluded because cervical vertebrae were not clearly detectable on lateral cephalometric x-ray. Another patient was excluded because no frontal x-ray was available.

Notably 9/18 of patients presented calcification of the atlanto-occipital ligament to various degrees. Among these, 7 patients presented a complete calcification, while 2, an incomplete one.

Calcification of the atlanto-occipital ligament was not correlated to gender nor age.

When compared to the other two sites of ossification, atlanto-occipital ligament calcification had a similar prevalence. Indeed, the prevalence was not statistically significant different as shown by chi-square test ($p=0.595$) (Table I).

Moreover, in 3 cases, atlanto-occipital ligament calcification represented the only sign of ectopic calcification, whereas in 6, it was concurrent with *diaphragma sellae* calcification, and in one case with *falx cerebri* calcification.

Discussion

Several studies on patients affected by NBCCS have described ectopic calcification of the skull as part of the syndrome (8, 10, 15). For this reason, NBCCS has been considered as a skeletal dystrophy syndrome. To the best of our knowledge, the presence of atlanto-occipital ligament calcification in patients affected by NBCCS has never been reported.

The etiology of atlanto-occipital ligament calcification remains uncertain. Since cartilaginous atlanto-occipital ligaments have been observed in fetuses and children (16), it had been postulated that it represents an acquired ossification of ligaments induced by the pulsation of the vertebral artery or an activation of existing osteogenetic potency in the region of the cranio vertebral junction. However, Prescher (17) discounted these previous theories.

The prevalence of complete or incomplete *arcuate foramina* has been studied extensively in skeletal bones (16), and radiographs (18-20). However, the reported prevalence relies on the method of the study. Indeed, it ranges between 9.5 and 15% for skeletal bone studies and between 2.6 and 14.3% for studies carried out on radiographs. Thus, even if the real prevalence of this calcification seems to be underestimate by x-ray examination, the highest value in bone studies is far from the prevalence reported here for NBCCS (50%). Here, patients affected by NBCCS showed an increased prevalence of atlanto-occipital ligament calcification than is found in the general population.

In our series, atlanto-occipital ligament calcification resulted was as common as *diaphragma sellae* and *falx cerebri* calcification, since the prevalence of these signs was not statistically different. Moreover, it can represent the only sign of ectopic calcification, as was the case in 3 patients of the studied population. Atlanto-occipital ligament calcification has the advantage of being detectable early in this disease (14) and of being easily detectable on lateral cephalometric x-ray, thus it could represent an extremely important aid in the early diagnosis of NBCCS in childhood, when, in the absence of major features such as BCC, jaw cysts, or *falx cerebri* calcification, which are often not evident until much later, other radiological manifestations of the disorder should be employed.

Although requiring further study to clarify this issue, the calcification of the atlanto-occipital ligament should be considered in addition to the other major criteria for diagnosis of NBCCS.

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