

Cervical Artery Dissection is Associated with Widened Aortic Root Diameter

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ABSTRACT: *Objective:* Dissection of the internal carotid and vertebral arteries is a well recognized cause of stroke, especially in the middle-aged. The exact etiology of this condition is controversial. According to one theory there is an underlying vasculopathy originating from disturbed development of the neural crest. The neural crest gives rise to several tissues, including the tunica media of large cervical arteries and the outflow tract of the heart. We attempted to test the theory that developmental abnormality at the level of the neural crest may play a role in dissection of the large cervical arteries. *Methods:* We designed a retrospective case control study. By means of transthoracic echocardiography we measured the aortic root diameter in a group of patients with radiographically determined dissection of at least one large artery in the neck. The results were compared to a control group. *Results:* In comparison to age matched controls, male patients were found to have a significantly larger aortic root. Although a similar trend was apparent in females, the difference between the patient and control group of females was not statistically significant. *Conclusions:* Patients with cervical artery dissections may have other abnormalities in organs arising from the neural crest. A larger prospective clinical study and further research are needed to establish a firm link between dissection of the cervical arteries and abnormalities in other organs.

RÉSUMÉ: La dissection des artères cervicales est associée à un plus grand diamètre de l'origine de l'aorte. *Objectif:* La dissection de la carotide interne et des artères vertébrales est une cause bien connue d'accident vasculaire cérébral, surtout dans la population d'âge moyen. L'étiologie exacte de cette condition est controversée. Une hypothèse propose qu'il existe une vasculopathie sous-jacente suite à un développement anormal de la crête neurale. La crête neurale donne naissance à plusieurs tissus, incluant la media des grosses artères cervicales et aux voies de chasse du coeur. Nous avons tenté de vérifier l'hypothèse selon laquelle une anomalie du développement au niveau de la crête neurale pourrait jouer un rôle dans la dissection des artères cervicales de gros calibre. *Méthodes:* Il s'agit d'une étude cas/témoins. Nous avons mesuré, au moyen de l'échocardiographie transthoracique, le diamètre de l'origine de l'aorte chez un groupe de patients ayant une dissection prouvée radiologiquement d'au moins une artère du cou de gros calibre. Les résultats ont été comparés à ceux obtenus chez un groupe contrôle. *Résultats:* Dans le groupe expérimental d'hommes, l'origine de l'aorte était significativement plus large que dans le groupe contrôle apparié pour l'âge. Bien qu'une tendance était évidente chez les femmes, la différence entre le groupe expérimental et le groupe témoin n'était pas significative. *Conclusions:* Il est possible que les patients qui ont une dissection d'une artère cervicale aient également d'autres anomalies des organes qui proviennent de la crête neurale. Une étude prospective de plus grande envergure et des recherches plus poussées seront nécessaires pour établir un lien entre la dissection des artères cervicales et des anomalies d'autres organes.

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Arterial dissection is a term applied to the phenomenon of cleavage along the layers of a blood vessel wall with consequent formation of clot within the wall itself. Dissections most commonly occur in the large arteries such as the aorta and its main branches. Large cervical arteries are affected less often while dissections of intracranial arteries are rare. In a large hospital only 1-3 vertebral dissections are diagnosed yearly.^{1,2} Carotid dissections are somewhat more common with an annual incidence rate of 2.5-3.0 per 100,000.³⁻⁵ Some authors believe that dissections are rather underdiagnosed in routine clinical practice and that they may cause up to 22 percent of strokes in young adults.⁶ Cervical artery dissections are multiple in 28 percent of cases with a recurrence rate of one percent per year.⁷

The etiology and pathogenesis of this condition are not clear. Classically, dissection was thought to be caused by hypertension

and trauma or neck torsion, but the real contribution of these factors is unknown. It has also been suggested that certain inherited connective tissue disorders (Ehlers-Danlos, Marfan syndrome, alpha-1-antitrypsin deficiency, osteogenesis imperfecta, fibromuscular dysplasia) make affected people prone to dissections,⁸ yet most patients with dissections have no signs of generalized connective tissue disorder and many of them have no history of preceding neck trauma.

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It has been posited that dissection starts with an intimal tear.⁹ In fact, pathological findings after a dissection include a tear in the arterial intima that spreads through the vessel wall creating a plane of dissection within the tunica media and, subsequently, forming a blood-filled pseudo lumen. The pseudo lumen may contain clot and may either expand and occlude the true lumen of the vessel or disrupt the innermost layer (intima) of the vessel and release clot into the main bloodstream. Rarely, the enlarging pseudo lumen may disrupt the entire arterial wall and cause an overt haemorrhage.⁵ Microscopic studies commonly reveal lesions like cystic necrosis and disorganized fibres in the tunica media of affected arteries.^{10,11}

More recent studies have searched for, and some have suggested the existence of, a more widespread disorder underlying artery dissection. A subtle disorder in connective tissue metabolism was suggested,^{12,13} and the discovery of familial cases of artery dissections¹⁴⁻¹⁶ led to several studies which unsuccessfully aimed to find a responsible gene(s).¹⁷ On the other hand, an increased incidence of bicuspid aortic valve in cases of familial dissections, an increased incidence of congenital heart disease in those with sporadic dissections,^{14,18} and skin lentiginosities in several family members suffering arterial dissections,¹⁵ lead to the suggestion that a neural crest defect may underlie at least some cases of arterial dissection.

In an attempt to test the hypothesis that arterial dissection arises from a "cristopathy", or abnormality in neural crest development, we have looked for an association between cervical arterial dissection and aortic root dilation. We limited our search to the aortic root in patients with radiographically proven dissection largely because of its accessibility to echocardiography. Despite the small groups of patients we were able to identify who satisfied all our entry and exclusion criteria, we showed a statistically significant association between cervical artery dissection and a wider aortic root, at least in men. Our data suggest that cervical artery dissection may be part of a wider syndrome.

METHODS AND PATIENTS

The study was designed as a retrospective case control evaluation of the association between clinically proven arterial dissection and the size of the aortic root. Using a computerized database at the Ottawa General Hospital (OGH) we identified patients whose discharge diagnosis was coded as artery dissection and who were treated either in the neurology or neurosurgery services. The period covered by the search was January 1993 – March 1997 inclusive. Upon identifying all the patients with carotid or vertebral artery dissection, verified by angiography and/or MRI/MRA, those who had transthoracic echocardiography (TTE) as part of their stroke work-up were selected. The transthoracic method of measurement is an acceptable standard for aortic root assessment.¹⁹ This method was also used in the present study because transesophageal echocardiography is not done routinely in all our stroke patients, whereas TTE is, and TTE has been used in previous studies of aortic root pathology.^{20,21} Their charts were then reviewed for a history of high blood pressure or other conditions which may be associated with aortic root dilatation (coarctation of aorta, aortic dissection, heart surgery). Those found to have such a condition were excluded. The remaining patients formed an experimental group whose aortic root diameter on echocardiogram was recorded.

Echocardiographic measurements were obtained with a commercially available ultrasound machine (HP 77020A; Hewlett-Packard Co., Andover, Mass.) with a 2.5 MHz phased array imaging transducer. Patients were imaged in the left lateral semirecumbent position. Aortic root measurements were acquired on-line in either the parasternal short or long axis views in the standard fashion according to ASE (American Society of Echocardiography) guidelines from M-mode tracings guided by two-dimensional imaging.

A control group of patients was selected from asymptomatic, normotensive patients who had been referred for an echocardiogram when a heart murmur had been heard by their physicians, but we ascertained by TTE that they were free of any structural heart abnormalities that could cause aortic root dilatation, such as valve disease, before they were included in the control group. The control and experimental groups were age and sex matched. The size of the aortic root is also affected by body size (height and weight). We do not have data on body size as this is not routinely collected for echo studies, but in a subset of patients where this information was available there was no statistical difference in body size.

Since we were testing if the aortic root diameter was larger in patients with arterial dissection, the difference in aortic root diameter between the experimental and control groups was tested by a single tail t-test. The threshold of significance was set at $p = 0.05$.

RESULTS

During the study period of 51 months, 49 patients were discharged from the OH-GS with a diagnosis of dissection of either the carotid or vertebral arteries. Twenty of these had a transthoracic echocardiogram done as a part of the stroke work-up. Four of these twenty patients were eliminated for purposes of this study: two because of a history of high blood pressure, and two because they were being treated with antihypertensive drugs. The remaining 16 patients were 7 men and 9 women, ranging in age from 41 to 64 years (mean 51.9) and 29 to 68 years (mean 42.6), respectively. There was no significant difference between the experimental and control groups with regards to age. Four males and 3 females were diagnosed with vertebral artery dissection, while the rest had internal carotid artery dissections. Four patients had a history of mild neck trauma. In eight cases the diagnosis was confirmed by both MRI/MRA and four-vessel angiography, six had an MRI/MRA only, and the remaining two had formal angiography. Figure 1 shows a selected example of dissection evident on angiography. The results of aortic root measurements in the experimental and control groups are summarized for men and women separately (Tables 1 and 2). A representative echocardiogram is seen in Figure 2. The difference in aortic root diameter between the experimental and control groups of males was significant (single tail t-test $p = 0.0128$). The same statistical test in the female groups revealed a p value of 0.0727.

DISCUSSION

Cervical artery dissection remains a puzzle. The patient usually presents with complaints of dull pain in the neck along the course of the affected vessel, and the clinical signs are often



Figure 1: A selected example of a right vertebral artery dissection diagnosed by angiography (arrow).

those of a stroke. The natural history of the condition is rather favourable: 85% of patients recover completely, and mortality is under 5%.⁵ Dissection of the intracranial portions of the carotid and vertebral arteries is a rare and more ominous condition with considerably worse prognosis.^{9,22-27}

Despite the relatively benign natural history of this condition, urgent medical attention is required. The diagnosis is confirmed by contrast angiography,^{2,11,28} but increasingly magnetic resonance angiography^{29,30} and even duplex Doppler ultrasound are useful in detection of dissections of the large lumen vessels.^{29,31} The goal of medical treatment is to prevent the complications of embolization from the clot formed within the wall of the affected artery, or rupture of the arterial wall due to enlarging hematoma. Anticoagulation followed by antiplatelet therapy is recommended.^{5,32}

The favourable outcome of most large arterial dissections belies our ignorance about the specific etiology in most cases. When trauma is suspected as the cause, it is often so minor as to raise the question why many more individuals exposed to the same trauma suffer no complications. An attempt at confirming a connective tissue disorder or collagen vascular disease in specific cases is usually fruitless. For these reasons, the suggestion

Table 1: Aortic root diameter in two groups of males.

Experimental group			Control group		
	Age	Dissection	Aortic root diameter, cm	Age	Aortic root diameter, cm
1.	52	ICA	3.8	62	2.9
2.	50	ICA	3.8	49	3.1
3.	41	ICA	3.6	54	3.3
4.	64	VA	3.0	52	3.1
5.	55	VA	3.1	41	3.1
6.	52	VA	3.9	55	3.4
7.	49	VA	3.7	47	3.0
8.				47	3.1
9.				56	2.9
10.				45	2.8
Mean	51.9		3.443*	50.8	3.070*
SD	6.9		0.428	6.2	0.183

*Single tail t-test: $p = 0.0128$

ICA = internal carotid artery, VA = vertebral artery

Table 2: Aortic root diameter in two groups of females.

Experimental group			Control group		
	Age	Dissection	Aortic root diameter, cm	Age	Aortic root diameter, cm
1.	48	ICA	2.7	28	2.6
2.	29	ICA	2.9	31	2.8
3.	30	ICA	2.4	41	2.1
4.	68	ICA	2.7	49	3.1
5.	45	ICA	2.7	39	2.4
6.	35	ICA	2.7	44	2.6
7.	30	VA	3.1	58	3.1
8.	39	VA	2.9	39	2.6
9.	59	VA	3.6	61	2.7
10.				29	2.2
Mean	42.6		2.856*	41.9	2.620*
SD	13.8		0.340	11.4	0.333

*Single tail t-test $p = 0.0727$

ICA = internal carotid artery, VA = vertebral artery

that cervical artery dissection may have a developmental origin appeared worth exploring and led us to test the hypothesis that cervical arterial dissections may therefore be associated with other developmental defects.

Our data reveal a positive association, only in males, between cervical artery dissection and widening of the aortic root. Although our initial data base identified 49 patients with dissection, the lack of echocardiography data limited our investigation to 20. Additionally, four of these were eliminated because they had hypertension, and we were concerned this condition may be an independent cause of aortic root enlargement. Despite this limited number of patients, the statistical correlation for males between a dissection event and the aortic root diameter was quite strong. Our hypothesis has since been confirmed in a similar case control study.²¹



Figure 2: Parasternal long-axis echocardiographic view of a patient with aortic root dilatation. M-mode cursor is at the level of the aortic root.

The neural crest is a transient embryonal structure that gives rise to many different types of cells and contributes to the formation of diverse organs, including melanocytes, portions of the heart and the tunica media of the aortic arch and its branches.^{14,15,18} Experimental studies have shown that the neural crest contributes to the development of the cardiac outflow tract,³³⁻³⁷ and the same seems to be true in humans.³⁸ The term “cardiac outflow tract” generally refers to the embryonal structure that functions as a sphincter at the arterial pole of the primitive heart which, at that stage, has not developed one-way valves. Subsequently, immigrating cells of the neural crest influence remodeling of the ventriculoarterial junction tissue.³⁹ In this study, the aortic root is looked at as part of the “ventriculoarterial junction”. The neural crest starts out as a group of nondifferentiated, multipotent cells that leave the neural tube immediately upon its closure. When the cells start to migrate, they do so in two directions – cranial and caudal. As they approach their definitive sites they become more and more differentiated. The cranial group of cells differentiates into ectomesenchyme and populates the pharyngeal arches. It gives rise to smooth muscle cells of the elastic arteries, fibrous tissue cells of the heart and face, pia mater and arachnoid, odontoblasts in the teeth and parts of the thymus and parathyroid glands. The caudal group does not differentiate into mesenchyme but into melanocytes of the skin, chromaffin cells of the adrenals, Schwann cells and sensory and autonomic ganglion cells.³⁸ Thus, the cranial neural crest cells form the aortic arch, cervical arteries, carotid body, coronary arteries, cardiac outflow tract and aortopulmonary septum.^{34,35} More precisely, the tunica media of the aortic arch arteries is made up of neural crest cells exclusively.⁴⁰

Experimental models have provided a precise description of the cardiac tissues resulting from the neural crest cells.³³ The ablation of different parts of the cranial neural crest of chick embryos leads to phenotypes with well defined cardiac and extra cardiac malformations.^{34,35,41} The presence of an intact

neural crest is also necessary for the development of vascular smooth muscle cells in the aorta and coronary arteries.⁴² Another component of the tunica media of large arteries – elastin – is also highly dependent on neural crest function. All the regions to which ectomesenchyme of cranial (cardiac) neural crest contributes are destined to become blood vessels of the elastic type.⁴³ Disruption of the neural crest at an early stage leads to impairment in the initiation and downstream propagation of elastogenesis.⁴⁴ Neural crest defects occurring later in embryogenesis affect only the spatial configuration of the elastin matrix.⁴⁴

In summary, our findings suggest that arterial dissections in the neck may in part be due to a developmental disturbance in the neural crest followed by a corresponding defect in phenotype. We suspect that the earlier the insult to the neural crest, the more severe and widespread the phenotypic defect. That may explain the rare association of dissections (cranial neural crest) with lentiginos (caudal neural crest) in some families. Perhaps our findings will induce others to confirm prospectively that cervical artery dissections are a part of a wider vasculopathic syndrome.

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