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1 **Title: Aortic tissue analysis in Turner syndrome**

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33
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39
40 **Keywords:** Turner syndrome; Aortic dilatation; Aortic Aneurysm; FISH analysis; Karyotype.

41
42 **Non-standard Abbreviations and Acronyms:**

43 AD: Aortic dilatation;
44 ASI: Aortic size index;
45 BAV: Bicuspid aortic valve;
46 ERCB: Ethics Review Committee for Biomedical research
47 FFPE: Formalin-fixed and paraffin-embedded;
48 MDC: Media degenerative changes;
49 MEMA: Mucoïd extracellular matrix accumulation (-I: Intralamellar and -T: Translamellar);
50 TAA: Thoracic aorta aneurysm.

51 Prevention of aortic dissection is difficult in patients with Turner syndrome (TS). The aim of
52 our study was to describe aortic walls' cytogenetics and histology in patients having a
53 prophylactic surgery for a thoracic aorta aneurysm (TAA).

54
55 TS affects 1/2500 female at birth ¹. In half of cases, a complete loss of one X-chromosome is
56 found in blood lymphocyte karyotype. A 45,X/ 46,XX mosaicism is present in 15-20% of
57 patients. A structural anomaly of the X chromosome (isochromosome, ring) is present in the
58 remaining patients.

59
60 Congenital heart abnormalities in TS include bicuspid aortic valve (BAV) and aortic
61 coarctation, in 20-30% and 15-20% of patients, respectively ². Aortic dilatation (AD) is
62 common in TS ³. The risk factors for aortic dissection are BAV, aortic coarctation, AD,
63 hypertension, a 45,X karyotype and pregnancy. According to the current guidelines ^{1,2},
64 prophylactic surgery is recommended to prevent any dissection event, when the ascending
65 aortic size index (ASI) is higher than 25 mm/m².

66
67 TS patients were recruited from our Reference Center for Rare Diseases ([Endo-ERN](#)). This
68 study was approved by the Paris North ERCB (N°12-029). Aortic histology and media
69 degenerative changes (MDC) score were assessed using a semi quantitative score ⁴. The X
70 monosomy was searched in blood karyotype, buccal smear and aortic media using
71 Fluorescence *in Situ* Hybridization (FISH). For each aortic tissue, one hundred cells
72 (media/adventice) were analyzed. These results were compared to data obtained from the
73 blood karyotype and buccal smears FISH results, when available. For one mosaic patient, an
74 additional FISH with TFE3 probe (Xp11.23) was performed on 50 nuclei to confirm the aortic
75 mosaicism.

76
77 Eleven aortic tissues from 11 patients were included. The patients' median age at prophylactic
78 aortic surgery was 39.0 years (IQR: 29.5-46.5). Their median age at TS diagnosis was 8.0
79 years (IQR: 2.8-13.0). BAV was present in 10/11 cases. According to Sievers' classification ⁵,
80 6/11 patients had a type 1 BAV, with one raphe and fusion of both coronary cusps (L-R).

81
82 The median ascending aortic diameter and ASI at surgery were 44 mm (IQR: 39.0-45.5) and
83 29.0 mm/m² (IQR: 26.7-30.1), respectively. The aortic surgical techniques were as follows:
84 Yacoub (5/11), Bentall (5/11) and Tyron-David (1/11).

85
86 The blood karyotypes showed: an homogenous X monosomy in 7/11 cases, a 45,X/46,XX
87 mosaicism in 1/11 and a structurally abnormal X chromosome in 3/11 cases (two X ring and
88 one Xq isochromosome).

89
90 An early MDC (**Figure 1A**) was found in all patients. The MDC score was 9.0 (IQR: 7-10.5).
91 It was characterized by a loss of smooth muscle cells, a mucoid extracellular matrix
92 accumulation (MEMA-I or/and MEMA-T), as well as loss and/or fragmentation of elastic
93 fibers.

94
95 In aortic media walls, the X monosomy was frequent, as it was present in 7/11 of cases. The
96 level of 45, X mosaicism was otherwise higher than 60%.

97
98 Interestingly, one patient (**Figure 1B**) with a low 45,X mosaicism in blood (5%), had a higher
99 rate of X monosomy (70%) in endothelial and muscle components of her ascending aortic
100 media.

101 To our knowledge, this is the first aortic FISH description in patients with TS having
102 prophylactic surgery. Histology revealed an early MDC in all cases, even in young TS
103 patients. Our group previously identified similar levels of MDC in the aorta of non-TS
104 patients with TAA, with or without BAV⁴. In TS patients, MDC was present, even with a low
105 percentage of 45,X monosomy in blood. Therefore, a low level of 45,X monosomy in blood
106 should not be reassuring concerning an aortic dissection risk.

109 References

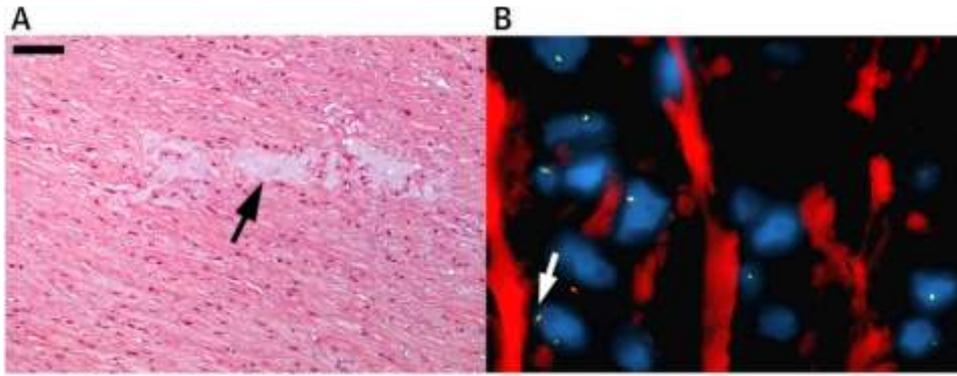
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129 Figure 1:

131 **1A:** Histology of an aortic wall showing a MEMA-T (arrow) and an aortic media multifocal
132 extension. Bar = 200 micrometers.

134 **1B:** FISH analysis on the FFPE section of an aortic tissue: A 45,X monosomy is found in the
135 majority of the nuclei of the aortic media (single green signal ; DXZ1 probe). In rare nuclei, 2
136 green signals are present (arrow).

138



139