

## **HEREDITARY VASCULOPATHY WITH DIFFUSE ISCHEMIC LESIONS OF THE NEVRAXIS (FOWLER SYNDROME): A RARE CAUSE OF FETAL AKINESIA**

**Fallet-Bianco, C** ; Yacoubi, TM ; Bazin, A ; Bessières-Grattagliano, B ; Beaufrère, AM ; Déchelotte, PJ.

**OBJECTIVES:** In 1972, Fowler described a new entity in five female siblings, all dead before 33 weeks, characterized by a unique proliferative vasculopathy and a hydrocephaly-hydranencephaly. The pathogenesis of this unique disease is yet unknown. We report the largest series studied so far of 6 cases with the aim of understanding the pathogenesis of this autosomal recessive condition.

**METHODS:** We performed a neuropathological and immunohistochemical study of 5 female foetuses and 1 male from 16 to 24 weeks old, in 5 families, including monozygotic twins. Parents were consanguineous in 3 out of 5 families.

**RESULTS:** The clinical phenotype was identical in all cases characterized by an early fetal akinesia sequence. Neuropathological examination disclosed diffuse clastic lesions of the nevraxis and the typical glomeruloid vasculopathy with characteristic PAS positive inclusions. Immunohistochemical studies showed an intense labelling of abnormal vessels with antibody directed against VEGF, an important angiogenic factor expressed in the neuroepithelium as soon as the fifth week. It enhances the proliferation of endothelial cells and the development of vessels. VEGF was expressed weakly and focally in age-matched controls. In addition, the nucleus of numerous cells was positive for HIF1 $\alpha$ , a transcription factor induced by hypoxia, which activates the transcription of genes encoding for proteins that increase the supply of oxygen including VEGF. Experiments have demonstrated that embryonic stem cells also express HIF1 $\alpha$  in normoxic situations for building the embryonic network. HIF1 $\alpha$  was not expressed in age-matched controls.

**CONCLUSION:** Our results lead to the conclusion that Fowler syndrome may result from an abnormally high expression of HIF1 $\alpha$  inducing an abnormal expression of VEGF and a proliferative vasculopathy. We suggest an inherited autosomal recessive anomaly involving either a gene controlling HIF1 $\alpha$  or a gene which when mutated leads to a HIF1 $\alpha$  over expression.

This document was created with Win2PDF available at <http://www.win2pdf.com>.  
The unregistered version of Win2PDF is for evaluation or non-commercial use only.  
This page will not be added after purchasing Win2PDF.