Intracranial vascular pathology in two further patients with Floating-Harbor syndrome: Proposals for cerebrovascular disease risk management

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ABSTRACT

Floating-Harbor syndrome (FHS) is a rare, heritable disorder caused by variants in the SRCAP gene. Most individuals with FHS have characteristic facial features, short stature, and speech and language impairment. Although FHS has been likely under-diagnosed due to a combination of lack of recognition of the clinical phenotype and limited access to genomic testing, it is a rare condition with around 100 individuals reported in the medical literature. Case series have been biased towards younger individuals (vast majority < 20 years of age) meaning that it has been challenging to provide accurate medical advice for affected individuals in adulthood.

We report two young adults with FHS who presented with intracranial haemorrhage likely secondary to cerebrovascular aneurysms, with devastating consequences, making a total of four FHS patients reported with significant cerebrovascular abnormalities. Three of four patients had hypertension, at least one in conjunction with normal renal structure. We consider possible relationships between hypertension, renal pathology and aneurysms in the context of FHS, and consider mechanisms through which disruption of the SRCAP protein may lead to vascular pathology.

We recommend that clinicians should have a low threshold to investigate symptoms suggestive of cerebrovascular disease in FHS. We advise that patients with FHS should have annual blood pressure monitoring from adolescence, renal ultrasound at diagnosis repeated in adulthood, and timely investigation of any neurological symptoms. For patients with FHS, particularly with hypertension, we advise that clinicians should consider at least one MRA (Magnetic Resonance Imaging with Angiography) to check for cerebral aneurysms.

1. Introduction

1.1. Floating-Harbor syndrome

Floating-Harbor syndrome (FHS) is a rare neurodevelopmental genetic condition associated with mutations in the SRCAP gene, which encodes the SNF2-related chromatin-remodelling ATPase (SRCAP) protein (Patton et al., 1991; White et al., 2010). Inheritance is autosomal dominant, though the vast majority of reported cases involve de novo mutations. SRCAP is thought have widespread effects on cell growth and division, affecting transcription, repair and replication of DNA via a role in chromatin remoulding (Messina et al., 2016). Most individuals with FHS have the typical features, described in Box 1 (Nikkel et al., 2013). Medical conditions previously associated with the condition have been summarised previously, and include renal pathology such as polycystic disease and hydronephrosis, growth hormone deficiency, precocious puberty, middle ear and ocular abnormalities (Reschen et al., 2012).

Two single patients with FHS have been previously reported with cerebrovascular aneurysms (Coughlin et al., 2017; Paluzzi et al., 2008); here we present a further two patients with cerebrovascular disease in young adulthood. We describe two patients who presented with acute intracerebral haemorrhage on a background of adult-onset hypertension, one with a confirmed right middle cerebral aneurysm and one with a suspected left middle cerebral aneurysm. We consider what impact these data have on clinical management of patients with FHS and provide suggestions for screening in adult patients with FHS.

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Box 1
The Floating-Harbor Phenotype.

- Characteristic facial features are the most distinctive features of the syndrome; triangular facies, a broad-based long nose with narrow bridge and overhanging tip, deep set eyes, low set ears and short philtrum
- Persistent short stature (final adult height typically 140–155 cm), though this may be dependent on whether growth hormone treatment was given.
- Speech development is usually delayed, typically expressive > receptive, with dysarthria and verbal dyspraxia, hypernasality and a high-pitched voice often observed.
- Low birth weight with a normal head circumference is commonly observed
- Early feeding difficulties and poor postnatal growth are often seen
- Bone age is often significantly delayed in early childhood but tends to normalise between the ages of 6–12 years.
- Skeletal abnormalities are variable but include brachydactyly, clinodactyly, prominent joints and swelling of fingertips (that appear clubbed), and short broad thumbs.
- Intellectual impairment is invariably present but typically ranges from mild to moderate. Gross and fine motor development usually normal.
- Challenging behaviour can be a feature with ADHD spectrum disorders, and sometimes aggressive and violent episodes that can be difficult to manage.

For detailed phenotyping data for FHS, see the analysis of 52 patients with FHS by Nikel et al. (Nikel et al., 2013).

2. Clinical report

We report two young adults with FHS presenting with intracerebral haemorrhage in adulthood thought to be secondary to cerebral aneurysms. In addition, we performed a literature review and summarise two previously published reports, each of a single patient with FHS and cerebrovascular aneurysm presenting in young adulthood. Our patients are described below, and the available data from all four patients is summarised in Table 1.

**Patient 1:** A female diagnosed with FHS in childhood, with typical features of the condition and a pathogenic variant in *SRCAP* (Table 1). She was diagnosed with hypertension as a young adult; this was controlled with ramipril. She had no known renal problems but did not undergo renal ultrasound. At 35 years she presented to medical services with a suspected first seizure (a sudden onset rigid and unresponsive episode) and unconsciousness, requiring ventilatory support. Computer Tomography (CT) scans showed a large intracerebral haemorrhage suspected to be secondary to a left middle cerebral artery aneurysm (Fig. 1A–C). After discussion with the family regarding the catastrophic impact of the haemorrhage, it was agreed that further medical treatment would not be of benefit and the patient later died. A post mortem was not conducted.

**Patient 2:** A male diagnosed with FHS in childhood, with typical features of the condition and a recurrent pathogenic mutation in *SRCAP* on genetic testing (Table 1). He had a normal renal ultrasound at 21 years of age and normal renal function. As a young adult he developed hypertension; this was controlled with ramipril. At 34 years he was found unresponsive following collapse, after previously been seen 12 h earlier. Head CT scans showed right temporal subarachnoid and intracerebral haemorrhage without hydrocephalus that was secondary to a right middle cerebral artery aneurysm. Treatment was with embolisation (coiling) of the aneurysm together with craniotomy for evacuation of the hematoma (Fig. 1D–F). Post-operatively there was temporary left-sided weakness and visual neglect with a post-operative right frontal lobe infarction; these clinical deficits subsequently resolved following rehabilitation. Nine months later the patient presented with a generalised tonic-clonic seizure and was commenced on long term anti-epileptic medication.

3. Discussion

Four adult patients have now been reported with cerebrovascular disease co-existing with FHS; this has involved identification of either intracerebral haemorrhage or cerebral aneurysms in all cases and an additional concern regarding a MoyaMoya phenotype in one case. Three of four patients were known to have hypertension requiring treatment in adulthood. None were known to have renal pathology though full clinical details are not available for the previously published two cases. Cerebrovascular aneurysms are rare in young adults and have a high mortality. Given that aneurysms are amenable to detection and intervention prior to rupture and that this improves outcome, we discuss appropriate recommendations for clinical care of patients with FHS.

**3.1. SRCAP and cerebrovascular disease**

Genome and exome sequencing of FHS patients has identified dominant negative mutations of the *SRCAP* gene as the predominant cause of the syndrome (Hood et al., 2012). The *SRCAP* protein is part of a chromatin remodelling complex that is highly conserved across species. Such complexes are capable of altering chromatin organisation through nucleosome displacement which then alters interaction between histones and DNA. This may alter the accessibility of nucleosomal DNA to DNA-binding proteins that have a role in transcription, repair and replication of DNA (Clapier and Cairns, 2009). Missense variants likely exert pleiotropic effects via an impact on chromatin and nucleosome organisation in addition to transcription and downstream signalling pathways.

Several recurrent mutations have been reported in *SRCAP*, such as those in exon 34 of the gene, including the mutation we describe in patient two, and these are thought to lead to protein truncation, leading to loss of terminal AT-hook DNA-binding motif domains (Hood et al., 2012). The AT-hook motif is found in many DNA-binding proteins that have a key role in chromatin organisation and gene expression, and disruption of this motif is predicted to alter protein function (Aravind and Landsman, 1998) although the mechanism of this is not yet known.

Independently to chromatin organisation, *SRCAP* is also thought to exert impact as a transcriptional regulator through its activation of the cAMP response-element-binding protein (CREBBP) which in turn activates a number of transcription factors and mediates widespread gene expression (Johnston et al., 1999). *SRCAP* is therefore able to influence multiple signalling pathways, such as the Notch signalling pathway and steroid-receptor mediated transcription pathways, in addition to its role in chromatin remodelling (Eisenberg et al., 2005; Monroy et al., 2003). There is considerable evidence that Notch signalling is critical to vascular development and has a role in vessel homeostasis in adults, including vascular repair (Wilson et al., 2016). Disruption of Notch signalling has already been implicated in the aetiology of intracranial aneurysms and arteriopathy, for example in Alagille syndrome (Tumialan et al., 2006).

Rubenstein-Taybi syndrome is a rare condition caused by mutations in the *CREBBP* gene which is closely-related to *SRCAP*, and shares considerable phenotypic overlap with FHS. Of note, both renal tract malformations and vascular pathology such as cerebral aneurysms have previously been reported in Rubenstein-Taybi syndrome, providing further evidence for a link between *SRCAP*, *CREBBP* and vasculopathy (Fischer et al., 2013).

In summary, *SRCAP* is well-placed to have diverse effects on cell growth including vascular development and homeostasis via its role in chromatin remodelling. In addition, there are other plausible mechanisms by which disruption of *SRCAP* function may lead to vascular
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Abbreviations: OFC – orbitofrontal circumference, BL – bilateral, y – year, m – month.
pathology, through transcription activation via CREBBP or downstream effects on Notch signalling pathways. Additional functional studies are needed to explore these hypotheses further, for example by measuring the impact of the presence of the truncated SRCAP protein on signalling pathways in cell lines derived from patients with FHS.

3.2. The role of hypertension in cerebrovascular disease

Three of the four described FHS patients with cerebrovascular disease were known to have hypertension in adulthood and this was sufficient to require pharmacological treatment in two patients. Renal pathology that may account for hypertension has previously been reported in some patients with FHS, for example polycystic kidney disease (Reschen et al., 2012). However, the aetiology of hypertension was not known for our patients – patient one did not have renal investigations prior to death, and patient two had a normal renal ultrasound in adulthood and normal renal function. The lack of renal imaging data in three of the four patients reported means it is difficult to know whether the hypertension in these four patients was of renal aetiology, however the findings in patient two who had hypertension in the context of normal kidneys suggests an alternative aetiology for hypertension in FHS at least in some cases.

The relationship between hypertension and cerebrovascular aneurysms is complex and may be different for individuals with FHS compared with the general population. Data assessing the aetiology and consequences of hypertension in patients with FHS with hypertension is minimal. However, of note recent large meta-analyses have indicated that in the general population, hypertension is not a risk factor for development and growth of cerebral aneurysms but that it is a risk factor for aneurysmal rupture and intracerebral haemorrhage (Brinjikji et al., 2016).

3.3. Cerebrovascular aneurysms

Although intracranial aneurysms are an occasional incidental finding in post mortem studies of the older population, they are very rare in children and young adults (Inagawa and Hirano, 1990). Rupture of cerebral aneurysms typically results in subarachnoid and intracerebral haemorrhage, often with resulting raised intracranial pressure and associated mortality. Prior to rupture, a significant proportion (> 50% in one case series) of cerebral aneurysms are completely asymptomatic (Raps et al., 1993), providing support for the use of screening neuroimaging, however the exact role of serial neuroimaging is not yet well-defined.

The risk posed by unruptured cerebral aneurysms has been widely debated; recent studies suggest that the risk is higher for posterior versus anterior circulation aneurysms, and that the five year cumulative rupture rate increases with aneurysm size, more rapidly above 7 mm diameter to as much as 40% for aneurysms over 25 mm (Wiebers et al., 2003). Critical review of the literature indicates that aneurysms larger than 5 mm in patients under 60 years of age should be seriously considered for treatment, whereas small aneurysms under 5 mm can be managed conservatively, typically with anti-hypertensives and smoking cessation where relevant (Komotar et al., 2008).

3.4. Cerebrovascular disease, short stature and growth hormone

Cerebral aneurysms and cerebrovascular disorders such as Moyamoya syndrome have been previously reported in other syndromes that also involve short stature and growth disturbance as occurs in FHS, for example in microcephalic osteodysplastic primordial dwarfism type 2 (MOPD II) (Bober et al., 2010).

This has often been attributed to shared genetic effects on both cell growth and vascular development in developmental disorders. MOPD II involves biallelic mutations in the gene PCNT, which encodes pericentrin, a centrosomal protein important for cell cycle progression. Similar to the Notch signalling proteins, pericentrin is also thought to be involved in vascular homeostasis, particularly with regard to inflammatory and infection-related environmental insults (Munot et al., 2011), which may explain the link with cerebrovascular aneurysms in both FHS and MOPD II.

However, it is also worth noting that many patients with short stature such as occurs in both FHS and MOPD II are treated with growth hormone. An association has been suggested between cerebral
anomalies and hypersecretion of growth hormone from pituitary adenomas, via growth hormone-induced changes in collagen in cerebral vessels (Oshino et al., 2013), suggesting that there could be secondary effects of growth hormone therapy on vascular structure. However, only two of the patients presented herein received growth hormone therapy for short stature, suggesting this is not a consistent association.

3.5. Implications for screening in FHS

The data described above and previously in the literature (Reschen et al., 2012; Coughlin et al., 2017; Paluzzi et al., 2008) describing associations between FHS and both renal and cerebrovascular pathology, though not necessarily co-existing within an individual, provide important evidence to suggest that regular blood pressure monitoring should be part of routine clinical care for FHS patients. We recommend that this should be done on at least an annual basis from adolescence; if hypertension is identified, blood pressure monitoring will be required more frequently. In addition, given the previously reported renal abnormalities associated with FHS (Reschen et al., 2012), a renal ultrasound scan at diagnosis and repeated in adulthood are also advised.

In addition, identification and treatment of asymptomatic unruptured aneurysms with neuroimaging screening may benefit this group of patients, particularly if hypertension has been identified, since it is a known risk factor for aneurysm rupture. We recommend that as a minimum, clinicians should request neuroimaging investigation of patients with FHS who develop any signs suggestive of cerebrovascular disease, such as headache, visual disturbance, seizures and focal neurological deficits. A high level of patient awareness is required to permit individuals to seek appropriately urgent medical attention in such circumstances; for patients with intellectual disability and speech impairments, accurate and timely communication of symptoms to a medical professional may be difficult.

The associated costs and impact of regular neuroimaging need to be considered; this is challenging for rare disorders like FHS where little data exist to assist. As a comparison, it has recently been recommended that patients with MOPD II, the short stature syndrome described above, should be offered neuroimaging surveillance for cerebrovascular disease, with magnetic resonance imaging every two years in adulthood (Perry et al., 2013). MRI with magnetic resonance angiography (MRA) would be in general favoured for screening over CT angiography. This avoids repeated radiation exposure and the use of contrast necessary for CT angiography. MRA is considered an appropriate method for detection of asymptomatic arteriopathy and the cost of MRA screening is at least partially offset by the high treatment costs associated with the high morbidity that results from untreated cerebrovascular disease. In addition, the psychosocial impact of increased screening for individuals with FHS should be considered. Increased visits to healthcare professionals for screening measures may lead to increased anxiety, and some individuals can find the process of undergoing MRI scans unpleasant. The balance between minimising the burden of screening versus the benefits of identifying serious but asymptomatic medical problems is challenging; more data are required to provide a specific optimal screening protocol.

However we advise that serious consideration be given to MRA serial screening for adults with FHS, particularly in patients with co-existing hypertension, and recommend that at least one MRA scan be undertaken in adult FHS patients with hypertension. More long term observational data are required to determine whether serial MRA screening is beneficial and to determine optimal intervals between scans, as normal vasculature at one time point does not necessarily exclude subsequent development of aneurysms.

4. Conclusions

We report two patients with FHS and cerebrovascular bleeds making a total of four published patients with FHS co-existing with cerebrovascular abnormalities. While three of these four patients were reported to have hypertension requiring medical treatment, none were known to have renal pathology although limited renal data were available for some patients. Obtaining adequately-powered prospective case control data regarding associated medical conditions is difficult for rare disorders. There is currently insufficient evidence in the literature to understand the relationship between hypertension, renal pathology and cerebrovascular aneurysms in FHS. However, the existing data suggests that these are all important associations with FHS.

We recommend that clinicians and patients should have raised awareness of symptoms such as sudden onset headache, visual disturbance, seizures or focal neurological deficits with a low threshold to investigate such symptoms promptly with neuroimaging. This requires both patient and clinician awareness to ensure this occurs in the required rapid timeframe. In addition, given that renal pathology and hypertension are frequently asymptomatic, we continue to advise blood pressure monitoring at least annually and a baseline renal ultrasound at diagnosis, repeated in adulthood. Following the reported cases of cerebrovascular aneurysms in patients with FHS, and that aneurysms are usually asymptomatic prior to rupture, we suggest that neuroimaging screening could benefit this cohort of patients, particularly if there is evidence of hypertension. We advise that at least one MRA scan is undertaken in patients with FHS and co-existing hypertension.

A specific link between SRCAP mutations and vascular pathology has not yet been confirmed. Further studies are required to identify how truncated proteins interact with wild-type SRCAP protein to disrupt its binding to DNA and chromatin targets, and to understand the further downstream effects on transcription activation and signalling pathways such as Notch. Additional in vitro functional studies of SRCAP alongside long-term observational follow up of patients with FHS will help to expand our understanding of the relationship between hypertension, cerebrovascular disease and renal pathology in this patient group.

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Declaration of competing interest

The authors declare no conflicts of interest.

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