NF1 in Other Organs

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8.1 Cardiovascular Complications of NF1

Cardiovascular disease is a common cause of mortality in NF1. Cerebrovascular disease can occur at any age, and the risk of childhood stroke, particularly haemorrhagic stroke, is significantly elevated [2]. Hypertension appears a strong risk factor for paediatric stroke in NF1, but less so for adult stroke. Abnormal arterial anatomy with ectatic or stenotic vessels and intracranial aneurysms is frequently seen. The internal carotid, middle cerebral or anterior cerebral arteries are most likely to be involved [3], with the appearance of moya moya a frequent consequence. This may be amenable to treatment by pial synangiosis, with a resultant improvement in outcome [3].

8.1.1 Hypertension

The incidence of hypertension in NF1 is higher than in age-matched general populations. This increase is especially notable in childhood, warranting lifelong 6–12 monthly surveillance from as early as is practicable. Dubov et al. [4] noted blood pressure recordings above the 95th centile for age in 20% of measurements made in a paediatric NF1 cohort, with 6% of patients having persistent hypertension. No association with obesity was identified. Renal artery stenosis and phaeochromocytoma are the most characteristic specific causes of hypertension to occur in association with NF1, but essential hypertension is common, accounting for over 50% of high blood pressure in this patient group. No difference in the management of essential hypertension is recognised between people with or without NF1, once underlying causes have been excluded.

8.1.1.1 Renal Artery Stenosis and Mid-Aortic Syndrome

Renal artery stenosis has been estimated to affect 2% of patients with NF1, and classically presents in childhood. It may be unilateral or bilateral. Renal revascularisation may be effective in managing this condition, which may be due to localised

fibromuscular dysplasia as in sporadic cases, or represent a manifestation of a more generalised NF1-associated vasculopathy. Compression of vessels by neurofibroma or diffuse neurofibromatous tissue has also been postulated as a mechanism for renal hypertension. Further manifestations of vasculopathy include aneurysms (in up to 30% of patients [5], with spontaneous rupture of accessory renal artery aneurysm reported [6], for example). Venous aneurysms may also occur [7].

NF1 is the commonest identified genetic cause of mid-aortic syndrome [8], a rare presentation which results from severe narrowing of the abdominal aorta and associated arteries, often associated with extensive vasculopathy elsewhere. Whilst a rare manifestation of NF1, it may be very difficult to treat if multiple vessels are stenosed, and result in severe hypertension, particularly if the renal vessels are involved.

8.1.2 Phaeochromocytoma

Phaeochromocytoma is estimated to affect 2% of patients with NF1 [9]. Tumours may present in childhood, though this is rare. NF1-associated phaeochromocytoma may present in a less typical manner than in patients without NF1. Hypertension may not be detected and the high prevalence of anxiety and other neurobehavioural features in NF1 can also confound the identification of adrenergic symptoms. Similar to observations of phaeochromocytoma in other contexts, the adrenal medulla is the commonest site of origin and 12% of NF1-associated phaeochromocytomas are malignant when examined histologically. Bilateral tumours appear rare. Compared to sporadic phaeochromocytoma, NF1-associated lesions are on average smaller when detected, with less evidence of hypertension, but this may reflect early diagnosis following a higher index of suspicion, or incidental detection on imaging performed for other reasons [10]. No strong familial aggregation of phaeochromocytoma in NF1 is recognised, but co-occurrence of other neuroendocrine tumours, most commonly within the gastrointestinal tract, is a recurrent observation. Non-functional adrenal adenomas are also a common finding in patients with NF1, and demonstrate biallelic loss of function of NF1, though such lesions are not rare in the general population. Plasma metadrenaline assay is a core investigation in assessing for phaeochromocytoma, though elevated values may be observed in the absence of a secreting tumour in patients who are very anxious, or on medication that results in increased metadrenaline, such as monoamine oxidase inhibitors or sympathetomimetics, necessitating repeat testing.

8.1.3 Congenital Heart Disease in NF1

Ras-MAPK pathway functioning is critical to cardiac development, particularly of structures arising from the endocardial cushion. Where NF1 is dysregulated, Ras-MAPK-mediated endocardial-mesenchymal transition and proliferation are disrupted [11]. The most commonly identified lesions are therefore similar to those observed in other germline disorders of the Ras-MAPK pathway, particularly pulmonary stenosis, atrial septal defects and hypertrophic cardiomyopathy. Estimates for the overall prevalence of congenital heart disease in NF1 vary. 2.3% of patients

with NF1 in the large early series of Lin et al [12] had a cardiac anomaly, and estimates consistently suggest that such findings are more common than the 0.5% prevalence observed in the general population. Much of this increased risk may be attributable to the congenital heart disease burden observed in patients with type I whole gene deletions [13], prompting the recommendation for specialist cardiological evaluation in these individuals in particular [14]. A low threshold for such investigations may be warranted in any patient with NF1, particularly if any clinical symptoms or signs are detected on routine history or examination. Complex congenital heart disease is uncommon in NF1, with only occasional reports of tetralogy of Fallot [12] and an absence of other complex defects that are relatively frequently observed in other congenital heart disease cohorts.

8.1.3.1 Pulmonary Stenosis

Pulmonary valve stenosis is present overall in 2% of patients with NF1, but the prevalence appears increased in certain families, particularly those with missense NF1 variants [15]. This is in keeping with the previous descriptions of 'Watson syndrome' or 'NF-Noonan syndrome', both of which can now confidently be attributed to pathogenic variants in *NF1* [15]. Pulmonary atresia or more complex congenital heart disease may also occur in such families. Pulmonary artery stenosis has also been recorded in patients with NF1.

8.1.3.2 Other Valvular Abnormalities

8% of 65 patients with NF1 studied by Incelik et al. [16] had mitral valve incompetence (n = 5), compared to population estimates of 1.2% [17]. Single patients in their cohort were found to have aortic regurgitation and tricuspid regurgitation, respectively. Aortic stenosis has also been reported [13]. Whether mitral valve abnormalities are associated with the joint hypermobility seen in a significant proportion of individuals with NF1 has yet to be established. In both the general population, and individuals with disorders of connective tissue, joint hypermobility commonly coexists with mitral valve prolapse [18].

8.1.3.3 Cardiac Septal Defects

The prevalence of atrial and ventricular septal defects appears increased in NF1, though definitive data are lacking, and the published literature may be subject to ascertainment bias. 3–4% of patients with NF1 studied in series have had secundum atrial septal defects identified [16, 19]. Unroofed coronary sinus, a rare cause of atrial septal defect, has also been reported in a single individual with NF1 [20]. Ventricular septal defects appear less common than atrial defects, with single patients reported in modestly sized NF1 cohorts, particularly those with whole gene deletion [13], suggesting a somewhat increased risk compared to the general population.

8.1.3.4 Hypertrophic Cardiomyopathy

Findings consistent with eccentric left ventricular hypertrophy have been reported in asymptomatic patients with NF1, namely increased left ventricular diastolic posterior wall thickness and intraventricular diastolic septal thickness [13]. The

significance of these remains unclear, but arrhythmias or more severe degrees of myocardial hypertrophy are not known to be associated with NF1, and hence their presence should prompt consideration of an additional cause. Foetal onset of hypertrophic cardiomyopathy, as may be observed in Noonan syndrome, has only extremely rarely been reported in association with NF1 [21].

8.1.3.5 Sudden Cardiac Death

Whilst fatal arrhythmias have not been attributed to NF1, sudden cardiac death, including in childhood, is a recurrently reported rare complication. Cardiovascular causes are a major source of the excess childhood mortality observed in NF1. Kanter et al. [22] reported two unrelated patients with coronary artery occlusion likely to be due to NF1-associated vasculopathy. The pathogenesis of vasculopathy in NF1 is incompletely understood, but is a recognised manifestation throughout the vasculature (see discussion of moya-moya in Chap. 13). Another patient with whole gene deletion was reported to have died suddenly at 16 years of age of myocardial infarction, with multiple coronary artery aneursyms identified at post-mortem [23]. The prevalence of coronary artery disease in the general adult population may lead to underascertainment of NF1-associated arteriopathy in patients with other identifiable risk factors. Intramyocardial vasculopathy as the likely cause of sudden death was reported in a 33-year-old patient by Hamilton et al. [24]. Within the vessels, regions of intimal thickening with high cellularity were present, as were areas of fibrotic, hypocellular lipid-poor plaque formation.

8.1.3.6 Intracardiac Tumours

Intracardiac tumours are very rarely reported in NF1. Two of 16 patients with whole gene deletion in Nguyen et al's [13] series had such lesions identified echocardiographically, and only one patient in the 2322 of Lin et al's cohort [12] was known to have such a tumour.

8.2 Lymphatic Abnormalities

Diffuse or plexiform neurofibromatous tissue may involve or disrupt lymphatic structures, and result in lymphoedema of affected parts. Resections for neurofibroma, or surgical or radiotherapy treatment of malignancy may also be risk factors for the development of lymphoedema. Whether or not primary lymphatic dysplasia (as is occasionally recorded in other germline disorders of the Ras-MAPK pathway) may also occur in NF1 is unclear.

8.3 Gastrointestinal

Gastrointestinal neoplasia is common in NF1, but the proportion of patients estimated to be affected ranges widely from 2 to 25% [25]. Common lesions associated with NF1 throughout the body, including neurofibromas and malignant peripheral

nerve sheath tumours (MPNST), may occur within the gastrointestinal tract. Hepatobiliary and/or pancreatic involvement by plexiform neurofibroma is well documented, particularly at the porta hepatis [26], but is rare. The incidence of gastrointestinal stromal tumours (GIST) and gut associated neuroendocrine tumours is greatly increased in NF1. The question of whether there is an increased risk of tumours more common in the general population, such as colorectal cancer, remains to be clarified (as discussed in Chap. 17).

Despite gastrointestinal tract neoplasia being relatively common, acute intestinal obstruction is a rare sequela of NF1. A systematic review identified intussusception (caused by GIST or neurofibroma), intrinsic obstruction by plexiform neurofibroma or stenosing colorectal carcinoma, and extrinsic obstruction caused by malignant GIST, plexiform neurofibroma or MPNST as recorded causes [27].

8.3.1 Gastrointestinal Stromal Tumours

GISTs arise in the gastrointestinal sub-mucosa, and are the commonest mesenchymal tumour in the GI tract, they are seen in up to 7% of patients with NF1 [28]. The natural history of these tumours diverges from that of sporadic GIST. At the molecular level, c-KIT, mutated in the large majority of sporadic GISTs, is not usually mutated in NF1-associated GIST, and inactivation of the wild-type NF1 allele appears crucial to the pathogenetic mechanism for these lesions, as is the case for other NF1-associated tumours. NF1-associated GISTs may behave in an indolent fashion, and surgery is not indicated for most lesions below 2 cm in diameter, though treatment options are more limited for advanced tumours as tyrosine kinase inhibition with agents such as imatinib, which can be effective adjuvant therapy for advanced c-KIT mutated GIST, may not be applicable. Regorafenib and sunitinib (other tyrosine kinase inhibitors) each have anecdotal evidence for efficacy in patients with NF1-associated GIST [29, 30].

An earlier age at diagnosis is seen than for non-NF1-associated GIST, and in contrast to sporadic GISTs, extragastric locations are more common. Multifocal GIST is associated with NF1, and this, in combination with ‘quadruple negative’ genotype (no c-KIT, PDGRFA, BRAF or SDH gene mutation identified), may be the presenting feature of hitherto unrecognised neurofibromatosis type I [31].

8.3.2 Neuroendocrine Tumours

Neuroendocrine cells exist throughout the GI tract, secreting gut regulatory hormones. Tumours arising from these cell lineages (neuroendocrine tumours, previously termed carcinoid tumours) affect a small percentage of people with NF1, and can present with consequences of hormone secretion, bleeding, local pressure effects (such as obstructive jaundice from an ampullary lesion [32]), or be identified incidentally on imaging. The most commonly secreted hormone in NF1-associated neuroendocrine tumours is somatostatin, and characteristic histological appearances

include psammomatous calcification [33]. Whilst the duodenum and ampulla are the region in which these have been most frequently recognised [34], the prevalence of lesions elsewhere in the GI tract may be underestimated.

Rarely, neuroendocrine tumours can present with carcinoid syndrome, namely facial flushing, diarrhoea, right-sided heart lesions, facial telangiectasia or bronchoconstriction, but this is caused when functionally secreting tumour tissue drains via extrasplanchnic vessels, which usually only occurs in metastatic disease. The possibility of such a tumour should be borne in mind for patients with NF1 presenting with such symptoms.

8.3.2.1 Gangliocytic Paraganglioma

Gangliocytic paraganglioma, a subtype of neuroendocrine tumour, is a very rare complication of NF1, which may have a favourable prognosis. It is most commonly located in the duodenum (90%), expression of progesterone receptor and pancreatic polypeptide is usual [35] and metastasis beyond lymph nodes is rare. Such tumours accounted for only 3% of duodenal lesions identified in patients with NF1 reviewed by Relles et al. [33].

8.3.3 Gastrointestinal Neurofibromas, Adenomas, Other Polyps and Carcinomas

Especially in patients with a high load of neurofibromas elsewhere, neurofibromas may be seen anywhere in or around the gastrointestinal tract. These may cause local effects or bleeding, but may be most likely to be identified incidentally on radiological or endoscopic imaging. Malignant tumours and premalignant adenomatous polyps of the gastrointestinal tract have not been recognised to be more common in patients with NF1, but the relative prevalence of colorectal carcinoma in the general population has potential to mask any subtle association by a lack of ascertainment of all relevant cases, as discussed in Chap. 17. The association of NF1 with juvenile-like hamartomatous polyp formation has also been reported [36].

8.4 GI Motility in NF1: Abnormalities of Structure and Function of the Enteric Nervous System

Dysmotility of the gastrointestinal tract is a common finding in the general population, and therefore it is unsurprising that it also occurs in many patients with NF1. Constipation is the most commonly reported symptom, and first line management is as for patients in the general population. However, the increased risks of gastrointestinal neoplasia and specific causes of dysmotility in patients with NF1 need to be borne in mind and appropriate thresholds for prompt investigation instituted. Exclusion of coeliac disease is important as, whilst no definite association is recognised, coeliac disease may coexist in at least 1% of patients with NF1 and is

treatable with a gluten free diet. Untreated coeliac disease may result in diarrhoea, anaemia and malaise and is an additional risk factor for small bowel malignancies such as lymphoma and adenocarcinoma.

Diffuse ganglioneuromatosis is a rare complication of NF1, also seen in Cowden syndrome (due to loss of function *PTEN* mutations) and multiple endocrine neoplasia type 2B (due to *RET* mutations). Presenting symptoms are varied, according to the site and extent of affected tissue, but may include bleeding, abdominal pain or refractory constipation. Whilst any organ supplied by the enteric nervous system may be involved, ileum, colon and appendix are most frequently identified to be involved. Biopsy demonstrates increased numbers of ganglion cells, Schwann cells and nerve fibres. Mucosal oedema and ulceration may be seen in affected regions. Coexistent plexiform neurofibroma of the mesentery has been reported in a patient with small bowel ganglioneuromatosis [37].

The rarity of such observations suggests that, whilst NF1 and MEN2B (in which such findings are more classical [38]), may be considered related neurocristopathies, further genomic and other factors are likely to be important in whether individuals with each of these conditions develop such manifestations. Further work is needed to determine the mechanisms of development and function of the enteric nervous system.

8.4.1 Gastroparesis

Gastroparesis is a troublesome condition that has anecdotally been reported in patients with NF1. It is plausible that autonomic nervous system dysfunction may underlie this, as is postulated in gastroparesis associated with diabetes mellitus [39], but the published literature in this area is sparse. Diagnosis is based on the combination of excluding mechanical causes of delayed gastric emptying and demonstrating objectively slow gastric transit by gastric emptying scintigraphy. An instance of gastroparesis presenting as a paraneoplastic phenomenon in a patient with NF1 has also been reported [40].

8.4.2 Irritable Bowel Syndrome and Constipation

Irritable bowel syndrome (IBS) is extremely common in the general population, but adults with NF1 have an even higher prevalence of such symptoms, with an odds ratio of around 3 for IBS and functional constipation [41]. In children, a small systematic study identified statistically significantly larger rectal diameter [42], and 20% of patients had an extended colonic transit time. Despite this strong association, there are few studies looking at the efficacy of specific interventions in patients with coexisting IBS and NF1, hence clinical management of IBS symptoms is similar to management of these in the general population, with the caveat that malignant pathology should be excluded as far as is possible in this group of patients.

8.5 Urogenital Features of NF1

Plexiform and diffuse neurofibromas involving the genitalia are unusual. Plexiforms involving the bladder and lower ureters have been reported somewhat more frequently, with the majority identified in males in early series [43]. The function of the urinary and genital tracts may be affected by adjacent pelvic neurofibromas or involvement of the nerve plexus supplying them. Urogenital malignancy risk in NF1, aside from pelvic MPNST, is not known to be elevated.

8.5.1 NF1 in the Genital Tract

Genital hypertrophy is recorded in association with NF1, but this literature is largely limited to case reports [44, 45]. Precocious puberty (affecting up to one-third of those with optic pathway glioma [46], and much less common in other children with NF1) may accentuate this. The internal or external genitalia may also be affected by the presence of neurofibromatous tissue and localised overgrowth observed [47]. Anecdotally, males with NF1 may be at a higher risk for cryptorchidism, as is the case for Noonan syndrome and other disorders of the Ras-MAPK pathway, but this is not a particularly rare phenomenon in boys in the general population and standard orchidopexy procedures are likely to be effective. Neurofibroma within the gonads appears extremely rare, with individual reports only [48]. Extensive plexiform neurofibroma involving multiple pelvic organs is a rare presentation that can be particularly challenging to manage.

Physiological aspects of fertility are not usually affected in individuals with NF1 unless pituitary or other endocrine problems are present. Sexual dysfunction may be prevalent for many, frequently interlinked, reasons including body image [49], other psychological factors and concurrent physical or mental health issues.

8.5.2 NF1 in the Urinary Tract

Congenital renal tract anomalies appear rare in NF1 [1]. Hydronephrosis may develop due to pelviureteric junction obstruction or ureteric compression by retroperitoneal neurofibroma [50]. Whilst plexiform neurofibromas of the urinary tract are rare, the bladder is the pelvic organ most commonly directly infiltrated by neurofibromatous tissue [51], and symptoms may include dysuria, haematuria and recurrent urinary tract infection. MPNST of the urinary tract appears, correspondingly, extremely rare, but has been reported [52].

Lower urinary tract dysfunction in NF1 may be due to plexiform neurofibroma involving the bladder wall, spinal cord or cauda equina involvement or compression, or central nervous system problems [53]. Obstruction of the urethra, as for the rectum or vagina, may occur due to extrinsic compression by neurofibromata [54]. Data regarding the prevalence of enuresis are not available, but, in keeping with the developmental delay observed in many children with NF1, it appears more prevalent than in the general paediatric population. A strong association of enuresis with

attention deficit hyperactivity disorder has been shown in population cohorts [55], in keeping with anecdotal observations in NF1, though a recent systematic review [56] concluded that further studies of this are required.

8.6 Pulmonary

Intrathoracic neurofibromas are the most common manifestation of NF1 within the chest, and can pose dilemmas in management, with significant risk of malignant transformation and a lack of symptoms until an advanced stage. The majority appear to occur in the posterior mediastinum adjacent to the pleura, but intercostal nerve involvement or endobronchial lesions are occasionally seen [57]. Neurofibromatosis-associated diffuse lung disease (NFDLD), like NF1-associated pulmonary hypertension, may cause significant morbidity and mortality.

8.6.1 Neurofibromatosis Type I-Associated Diffuse Lung Disease

NFDLD is characterised by apical cystic or bullous change, and basal fibrosis witnessed by ground glass and reticulate appearances on imaging [58]. The cystic changes can increase the risk of pneumothorax and, where more widespread emphysematous or fibrotic changes are present, chronic respiratory failure.

8.6.2 NF1-Associated Pulmonary Arterial Hypertension

Pulmonary arterial hypertension in NF1 is infrequent but may be associated with a poor prognosis. Where present, it usually, but not exclusively, occurs in the setting of interstitial lung disease, and age at presentation is older than for other subtypes of pulmonary hypertension [59]. The response of patients with PH-NF1 to pharmaceutical therapies for pulmonary hypertension is not known, and early consideration of transplantation has been suggested [59], with the caveat of taking into account the increased malignancy risk that may apply to patients with NF1 receiving immunosuppressant medication. The observation of NF1 patients with pre-capillary pulmonary hypertension (who have no evidence of interstitial lung disease) suggests that PH-NF1 may be a manifestation of NF1-associated vasculopathy [60]. As for other forms of NF1-associated vasculopathy, the molecular and cellular mechanisms underlying this remain incompletely understood.

8.7 Haematological

The principal haematological association with NF1 is juvenile myelomonocytic leukaemia (JMML). JMML is, as discussed in Chap. 17, a rare myeloproliferative disorder characterised by Ras-MAPK pathway dysfunction, with 90% having an

identifiable mutation in *NRAS*, *KRAS*, *PTPN11*, *NF1* or *CBL* [61]. Across JMML, driver mutations in *NRAS*, *KRAS* and *PTPN11* are usually somatic, whilst *NF1* and *CBL* often exhibit biallelic mutation, with the first 'hit' being in the germline. Whilst spontaneous remission may occur in 15% of JMML, patients with NF1 are likely to have progressive disease for which haematopoietic stem cell transplantation is required. The exact risk of JMML in NF1 is difficult to quantify, but recent Finnish cohort data suggests that this may be lower than previously thought, as no leukaemias were identified in 8376 person years of individuals with NF1 up to the age of 20 [62]. An association between juvenile xanthogranuloma (JXG) and JMML has long been recognised: it appears that NF1-associated JMML is seen almost exclusively in patients with JXG, though the risk for any individual patient with such lesions of developing JMML is only modest. Clinical surveillance with awareness of potential presenting symptoms of JMML is therefore required, and regular blood monitoring may also be considered [63]. The association of other haematological malignancies in NF1 is less conclusive, as discussed in Chap. 17, but the observation that 8/4939 children with ALL enrolled in the AIEOP-BFM ALL 2000 trial were known to have NF1 is compatible with a modest increase in risk [64] .

8.8 Glomus Tumours

Glomus tumours are very small mesenchymal lesions (only a few millimetres in diameter) that originate from the glomus body, a thermoregulatory shunt often located in the nail bed of the distal phalanx in fingers and toes. In the past, glomus tumours were often not diagnosed or misdiagnosed in NF1 patients, since it was thought that the pain was caused by an upstream neurofibroma affecting the nerve. The classical triad of glomus tumour symptoms include pain, localised tenderness and cold intolerance. Until 2009, only a few NF1 cases with glomus tumours were described and it was not clear if such lesions were part of the NF1 spectrum. In 2009, Brems and colleagues described 11 NF1 patients with glomus tumours, of which 5 presented with multifocal lesions [65]. The mean age was 40 years with a female predominance. Biallelic *NF1* inactivation was detected in the alpha-smooth muscle actin positive cells of the glomus tumour, resulting in over activation of the Ras-MAPK pathway after stimulation. Mitotic recombination of chromosome arm 17q has been detected in 22% of molecularly characterised NF1-associated glomus tumours [66]. To date, about 50 NF1-associated glomus tumour cases have been described in the literature [67, 68], but it has been estimated that glomus tumours may affect up to 5% of adult NF1 patients [69]. Glomus tumours can be clinically diagnosed with physical examination (e.g. pin-point pain) and a single question about the occurrence of pain in a digit during cold weather. The nail and pulp of the affected digit is often normal, MRI may demonstrate the lesions [69]. Surgical removal of symptomatic glomus tumours under local anaesthesia with or without sedation is the only effective treatment and may be curative. In general, the recurrence risk is low; however, when the bone is affected curettage is advised and the recurrence risk might be higher. Glomus tumours are almost always benign histologically.

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