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Lifelong Management of Neurofibromatosis 1 Patients

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Neurofibromatosis type 1 (NF1) is a prevalent genetic disorder characterized by a wide spectrum of clinical manifestations, including cutaneous, neurological, and oncological complications. The disease results from mutations in the NF1 gene, which encodes neurofibromin, a tumor suppressor that regulates the RAS/mitogen-activated protein kinase (MAPK) pathway. The loss of neurofibromin function predisposes individuals to both benign and malignant neoplasms, including malignant peripheral nerve sheath tumors, optic pathway gliomas, and gastrointestinal stromal tumors. Additionally, women with NF1 are at a significantly increased risk of developing breast cancer at a younger age, necessitating enhanced surveillance measures. Beyond oncological risks, NF1 is frequently associated with cognitive and behavioral impairments, including learning disabilities, attention-deficit hyperactivity disorder, and social communication difficulties, which significantly impact academic, occupational, and social outcomes. Moreover, systemic complications such as skeletal deformities, cardiovascular abnormalities, and chronic pain further contribute to the disease burden. Given the progressive and lifelong nature of NF1, comprehensive care strategies incorporating multidisciplinary management, early detection, and targeted interventions are essential to optimizing patient outcomes. This review highlights the importance of an integrative, lifelong management approach that addresses both the medical and psychosocial aspects of NF1. By implementing tailored surveillance programs and evidence-based interventions, healthcare providers can improve quality of life and reduce morbidity and mortality associated with this complex disorder.

Key Words : Neurofibromatosis 1 · Neoplasms · Cognitive dysfunction · Early detection of cancer · Quality of life.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder with an autosomal dominant inheritance pattern, affecting approximately 1 in 3000 individuals worldwide[24]. The condition arises from pathogenic mutations in the NF1 gene, which encodes neurofibromin, a tumor suppressor protein that regulates cell growth through the RAS/mitogen-activated protein kinase (MAPK) pathway. This dysregulation leads to the development of benign and malignant tumors as well as various non-tumor manifestations, significantly impacting the lives of affected individuals[19].

The clinical presentation of NF1 is highly variable, ranging from dermatological features such as café-au-lait macules and cutaneous neurofibromas to complex systemic complications. These complications include plexiform neurofibromas, optic pathway gliomas (OPGs), and an increased risk of malignancies such as malignant peripheral nerve sheath tumors (MPNSTs), gastrointestinal stromal tumors (GISTs), pheochromocytomas (PCCs), rhabdomyosarcomas and an increased risk of hemato-

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logic malignancies such as juvenile myelomonocytic leukemia (JMML)[28,47]. Recent studies have highlighted the elevated risk of breast cancer in NF1 patients, particularly in women under 50 years of age[57].

Population-based studies have consistently demonstrated that individuals with NF1 experience a shortened lifespan, with median life expectancy reduced by approximately 10 to 15 years compared to the general population[15,44]. Malignancies represent the leading cause of premature death in this population, particularly MPNSTs, which carry a poor prognosis[44]. Other contributors to mortality include vascular complications, such as cerebrovascular disease and hypertension-related events, as well as central nervous system tumors, including high-grade gliomas in children and OPGs with aggressive behavior[15,60]. Mortality is especially elevated in patients with early disease onset, high tumor burden, and among males[44,51].

Beyond physical manifestations, NF1 patients frequently experience cognitive and behavioral challenges, including learning disabilities, attention-deficit hyperactivity disorder (ADHD), and social communication difficulties, which further compromise their quality of life[12]. Studies estimate that 50–80% of NF1 patients exhibit some form of neurocognitive impairment, with executive dysfunction, visuospatial deficits, and emotional dysregulation being commonly observed[27]. Additionally, NF1 patients have an increased risk for psychiatric disorders such as anxiety and depression, particularly during adolescence and adulthood[35].

Effective NF1 management requires lifelong, stage-specific surveillance and intervention. Given the chronic nature of the disorder and its progressive complications, early detection and proactive management are essential to minimize morbidity and mortality. Regular monitoring is necessary for tumor progression, vision loss, hypertension, skeletal abnormalities, and hematologic disorders. Surveillance strategies must be tailored to different life stages, with pediatric patients requiring frequent ophthalmologic evaluations for OPG detection, while adolescents and adults benefit from breast cancer screening and cardiovascular assessments[16]. Advances in imaging modalities, biomarker research, and targeted therapies such as mitogen-activated protein kinase kinase (MEK) inhibitors have shown promise in treating plexiform neurofibromas and other NF1-associated complications. However, their long-term efficacy and safety profiles require further investigation[29].

The lifelong burden of NF1 extends beyond individual health concerns, affecting families and healthcare systems. Patients and caregivers face substantial psychological, educational, and social challenges, underscoring the importance of a multidisciplinary approach to care. Integrating genetic counseling, specialty care, psychosocial support, and patient advocacy programs is essential to address the diverse needs of NF1 patients and their families. Additionally, age-specific surveillance protocols and personalized therapeutic strategies are crucial to optimizing outcomes and improving quality of life. Understanding and addressing these multifaceted needs is critical to enhancing both health outcomes and overall well-being for NF1 patients[26].

This review aims to provide a comprehensive overview of the lifelong management of NF1, with a particular focus on the challenges associated with cognitive and behavioral issues, the risk of systemic malignancies, and the development of effective surveillance programs. By highlighting these aspects, this paper seeks to underscore the necessity of an integrative approach to enhance the quality of life and reduce the disease burden in this population.

CANCER PREDISPOSITION IN NF1

Patients with NF1 exhibit an increased risk of malignancies due to the loss of function of the NF1 gene, which encodes neurofibromin, a tumor suppressor protein involved in the regulation of cell proliferation and differentiation[19]. The cumulative lifetime malignancy risk in NF1 patients is estimated to be between 8–15%, significantly higher than in the general population[16]. The malignancies most frequently observed in this population include MPNSTs, OPGs, GISTs, JMML, rhabdomyosarcoma, PCCs, and breast cancer[28,29,47,57]. These malignancies, along with their prevalence, median age of onset, and surveillance strategies, are summarized in Table 1[10,37,42,49].

Among these, MPNSTs are particularly aggressive, with an incidence of approximately 10% among patients with plexiform neurofibromas[58]. These tumors often arise during adolescence or early adulthood and are associated with poor prognosis, with a 5-year survival rate ranging from 20–50%[30]. Their resistance to conventional chemotherapy and radiation therapy further complicates management, emphasizing the importance of early detection through routine physical examinations and imaging, particularly magnetic resonance imaging (MRI) for

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Table 1. Key malignancies in NF1

Malignancy	Prevalence (%)	Typical age of onset	Surveillance Strategies
MPNST	8–15	Adolescence to early adulthood	Annual physical exam, MRI for large plexiform neurofibromas
OPG	15–20	Childhood	Annual ophthalmologic exam in children, MRI if symptomatic
JMML	<1	Early childhood	Screening not indicated, juvenile xanthogranulomas warrant caution only
Rhabdomyosarcoma	Higher than general population	Variable	Routine physical examination, MRI for suspected masses
GIST	5–25	Middle adulthood	Gastrointestinal imaging/endoscopy if symptomatic
PCC	0.1–5.7	30–50 years	Annual BP monitoring, biochemical testing if hypertensive
Breast cancer	2–4	<50 years	Annual MRI/mammography starting at 30 years

NF1 : neurofibromatosis type 1, MPNST : malignant peripheral nerve sheath tumor, MRI : magnetic resonance imaging, OPG : optic pathway glioma, JMML : juvenile myelomonocytic leukemia, GIST : gastrointestinal stromal tumor, PCC : pheochromocytoma, BP : blood pressure

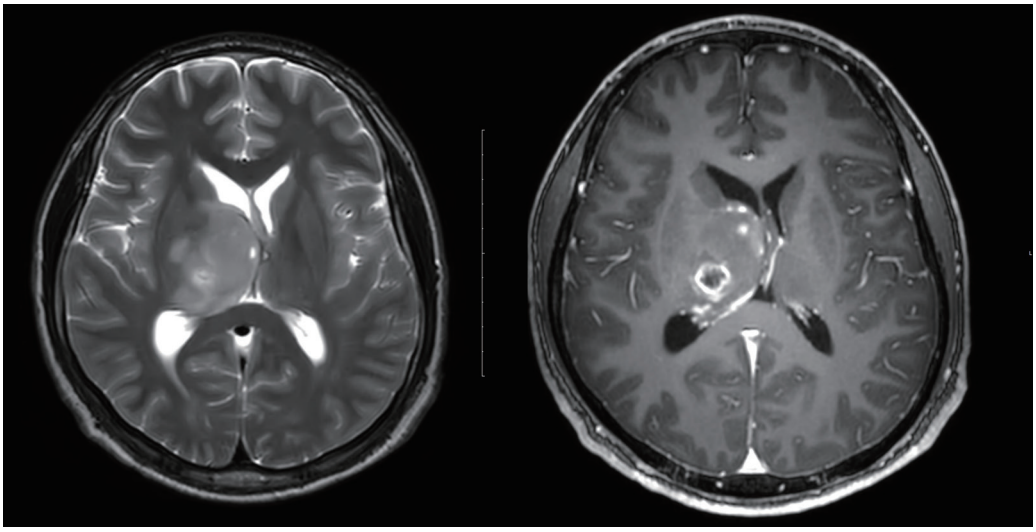

Fig. 1. Magnetic resonance imaging findings in an 18-year-old male patient with neurofibromatosis type 1, diagnosed with high-grade glioma. Axial T2-weighted image (left) shows a hyperintense lesion involving the right corona radiata and thalamus. Contrast-enhanced T1-weighted image (right) reveals cystic changes with peripheral enhancement. The patient was diagnosed with high-grade glioma based on stereotactic biopsy.

patients with large plexiform neurofibromas[16].

OPGs are one of the most common central nervous system tumors in NF1, with a prevalence of 15–20% among NF1 children[34]. These tumors typically manifest as low-grade pilocytic astrocytomas (World Health Organization grade I) and predominantly affect the optic nerve, chiasm, and hypothalamus[5]. While many OPGs remain asymptomatic, approximately 30–50% of affected children develop progressive visual impairment, proptosis, or hypothalamic dysfunction[3]. Routine ophthalmologic evaluations, including annual visual assessments in early childhood, are essential for early detection, with MRI being warranted in cases of declining vision or other concerning symptoms[16]. Given the potential for visual impairment to significantly impact daily functioning and educational attainment, early intervention with optical aids and supportive educational programs plays a crucial role in improving quality of life[3].

High grade gliomas (HGGs) are relatively rare but clinically significant. HGGs in NF1 patients typically present in adolescence or adulthood. Clinical observations suggest that thalamic gliomas in NF1 are more frequently associated with high-grade pathology (Fig. 1)[8]. Moreover, tumors located in the thalamus, frontal lobes, and cerebellum appear to have a higher likelihood of requiring surgical intervention[8]. Recent genomic profiling has identified NF1 deficiency as a defining alteration in a subset of isocitrate dehydrogenase (IDH)-wildtype glioblasto-

mas, which may confer sensitivity to targeted therapies such as MEK inhibitors[11]. In the absence of formal guidelines for this population, closer imaging follow-up may benefit NF1 patients with tumors in these regions.

Beyond nervous system tumors, patients with NF1 may have an elevated risk of hematologic malignancies, particularly JMML, a rare and aggressive myeloproliferative disorder that primarily affects young children and carries a poor prognosis[47]. Although JMML is overrepresented in children with NF1, the absolute risk remains low—likely less than 1%—and specific screening or surveillance strategies are not currently recommended[10]. Juvenile xanthogranulomas (JXGs), which are benign yellowish skin nodules seen in a subset of young children with NF1, were previously suggested to be associated with increased leukemia risk[61]. However, subsequent studies indicates that JXGs are either not a risk factor for leukemia or the risk is too low to justify targeted evaluation[9,17]. Therefore, JMML screening should not be conducted solely based on the presence of JXGs. Some degree of clinical vigilance may be appropriate in NF1 patients, particularly in the presence of concerning signs such as pallor, hepatosplenomegaly, lymphadenopathy, or unexplained bruising[10].

Another malignancy with increased prevalence in NF1 is rhabdomyosarcoma, an aggressive soft tissue sarcoma that arises from skeletal muscle progenitors. NF1-associated rhabdomyosarcoma typically presents in the genitourinary tract or head and neck regions, often demonstrating the embryonal subtype[47]. Although specific rhabdomyosarcoma surveillance guidelines for NF1 patients are lacking, regular physical examinations focusing on soft tissue abnormalities are advised, with imaging studies such as MRI recommended for any suspicious or rapidly enlarging masses[37]. The burden of rhabdomyosarcoma treatment, which includes chemotherapy, radiation therapy, and surgical resection, is substantial, affecting both physical function and psychological well-being. Post-treatment rehabilitation and psychological support are essential components of long-term care.

GISTs in NF1 are distinct from sporadic GISTs, both in their molecular pathology and clinical presentation. NF1-related GISTs commonly arise in the small intestine, are often multifocal, and tend to present in middle-aged adults[36]. The clinical symptoms of NF1-GISTs include abdominal pain, gastrointestinal bleeding, and bowel obstruction, necessitating surgical intervention in symptomatic cases[6]. Although routine endoscopic or radiologic screening for asymptomatic NF1 patients is not universally recommended, early diagnostic imaging and endoscopic evaluation are essential for individuals experiencing gastrointestinal symptoms[16]. Chronic pain and bleeding associated with GISTs can significantly impact quality of life, reinforcing the importance of timely surgical resection and effective pain management strategies[36].

PCCs and paragangliomas (PGLs) occur in 0.1–5% of NF1 patients, with a peak incidence in the third to fifth decades of life[59]. These tumors, arising from chromaffin cells of the adrenal medulla (PCCs) or extra-adrenal ganglia (PGLs), lead to excessive secretion of catecholamines, causing episodic hypertension, tachycardia, and diaphoresis[4]. Annual blood pressure monitoring is recommended for adults with NF1. Elevated readings or symptoms suggestive of PCCs/PGLs should prompt biochemical testing and imaging studies[16]. Undiagnosed PCCs/PGLs can lead to severe cardiovascular complications, affecting both morbidity and mortality. Early diagnosis and management, including surgical intervention, significantly improve long-term outcomes[18].

Women with NF1 have a 2- to 4-fold increased risk of breast cancer, particularly before the age of 50[57]. This elevated risk is thought to stem from neurofibromin loss, which leads to unregulated RAS/MAPK signaling, a known driver of tumorigenesis in breast cancer[25]. Despite these increased risks, many NF1 patients do not receive appropriate cancer screening due to a lack of awareness. Current guidelines recommend annual breast MRI and/or mammography starting at age 30 to facilitate early detection[10]. Adherence to these surveillance protocols is crucial, as early diagnosis significantly improves treatment outcomes and survival rates, ultimately reducing the psychological and physical burden associated with breast cancer in NF1 patients[25].

The malignancy spectrum in NF1 is diverse, necessitating a nuanced approach to surveillance and management. While MPNSTs and breast cancer represent the most life-threatening malignancies, other tumors such as OPGs, GISTs, and PCCs require targeted monitoring at different life stages. Fig. 2 illustrates the age-specific tumor surveillance strategies in NF1 patients, highlighting key malignancies that require monitoring across different life stages. The implementation of age-specific surveillance protocols, coupled with tumor-specific treatment approaches, is essential for optimizing patient outcomes. Advances in targeted therapies, such as mechanistic target of rapamycin kinase (mTOR) inhibitors for OPGs and MEK inhibi-

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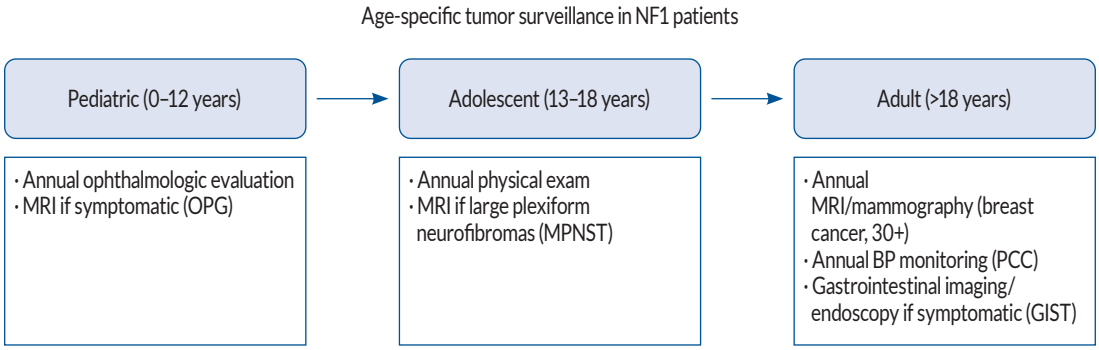

Fig. 2. Age-specific tumor surveillance in neurofibromatosis type 1 (NF1) patients. OPG : optic pathway glioma, MPNST : malignant peripheral nerve sheath tumor, PCC : pheochromocytoma, GIST : gastrointestinal stromal tumor.

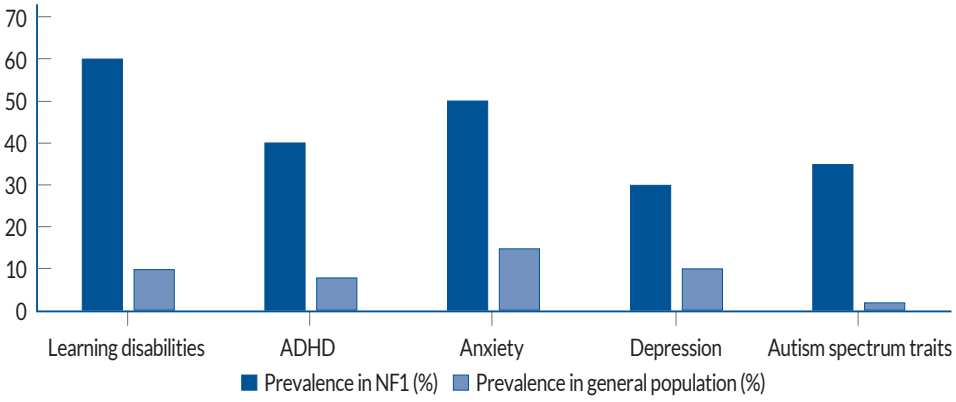

Fig. 3. Prevalence of cognitive and behavioral issues in neurofibromatosis type 1 (NF1) versus general population. ADHD : attention-deficit hyperactivity disorder.

tors for NF1-GISTs, hold promise for improving clinical management, while surgical interventions remain the cornerstone of treatment for PCCs and breast cancer. Through comprehensive and proactive surveillance strategies, clinicians can mitigate disease burden and enhance the quality of life for NF1 patients.

COGNITIVE AND BEHAVIORAL PROBLEMS IN NF1

Cognitive and behavioral impairments in NF1 can significantly impact quality of life across all stages of life. Cognitive and behavioral impairments are among the most common non-tumor manifestations of NF1, affecting approximately 50–80% of patients[12,27]. The most frequently observed cognitive deficits include learning disabilities, ADHD, executive dysfunction, and visuospatial impairments[41]. These challenges often emerge in early childhood and persist into adulthood, significantly impacting academic performance, social interactions, and occupational success[1].

Beyond cognitive impairments, behavioral and psychiatric conditions are also prevalent in NF1 patients. Studies have reported that children with NF1 exhibit higher rates of ADHD (40–50%), autism spectrum disorder-like traits (30–40%), and emotional dysregulation compared to age-matched controls[21]. Additionally, NF1 patients are at an increased risk for anxiety (30–60%) and depression, particularly during adolescence and adulthood (Fig. 3)[35]. These issues underscore the need for early screening and targeted interventions.

Hyperactivation of RAS signaling due to loss of regulation by neurofibromin in NF1, leading to abnormal synaptic plasticity and myelination defects[13]. Studies using NF1 mouse models have demonstrated that excessive RAS signaling contributes to

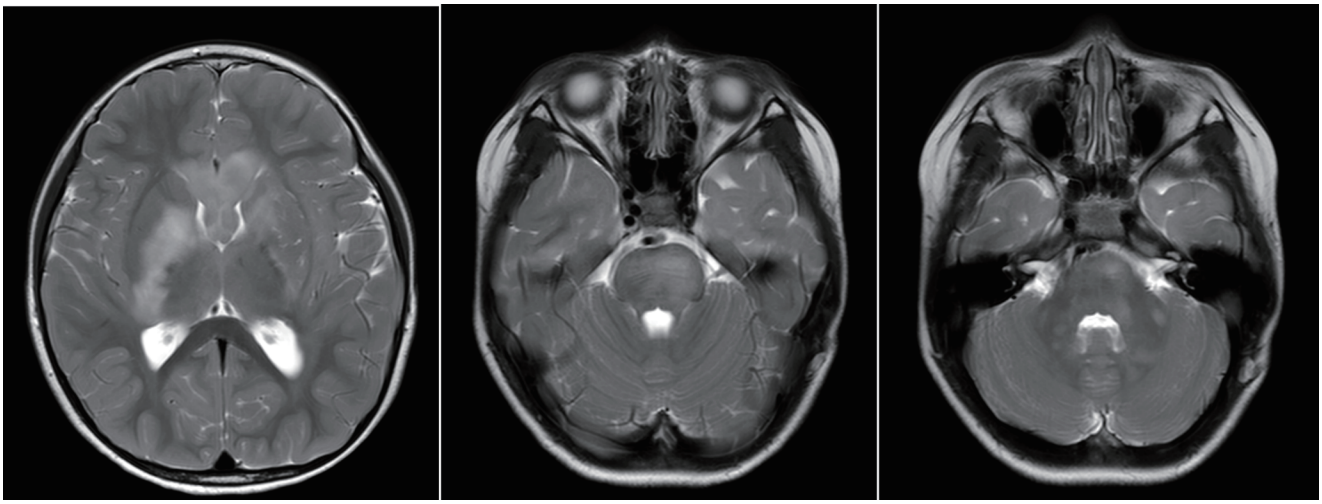

Fig. 4. Brain magnetic resonance (MR) imaging of a 4-year-old female with neurofibromatosis type 1 (NF1) showing optic pathway glioma (OPG) and focal areas of signal intensity (FASI). T2-weighted axial MR images demonstrate an OPG extending to the fornix (left image). Additionally, multiple FASIs are present in the right corona radiata and internal capsule (left), pons (center) and cerebellar peduncle (right), which are commonly observed in NF1 patients.

impairments in long-term potentiation and hippocampal-dependent learning, explaining the deficits in memory and spatial learning observed in NF1 patients[33].

Neuroimaging studies have also provided insights into the neural basis of cognitive dysfunction in NF1. Volumetric studies indicate reduced frontal and parietal lobe gray matter, correlating with executive dysfunction and attentional deficits[54]. However, the relationship between focal areas of signal intensity (FASI), also known as unidentified bright objects, and cognitive function in NF1 remains controversial. Some studies suggest that FASI presence, particularly in the thalamus and cerebellum, is associated with deficits in working memory and motor coordination (Fig. 4)[41]. Furthermore, larger and more numerous FASI lesions have been correlated with more severe cognitive impairments, such as executive dysfunction and attentional deficits[22,38]. However, other research indicates that FASI may not be directly responsible for cognitive decline but rather represent transient imaging findings that do not necessarily impact long-term neurocognitive outcomes[52]. Moreover, studies have shown that NF1 patients without FASI also experience cognitive deficits, suggesting that broader neurobiological mechanisms, such as RAS/MAPK pathway dysregulation, play a more significant role in cognitive impairment[27]. Therefore, while FASI may contribute to neurocognitive variability in NF1, it is crucial to consider the broader neurodevelopmental context when assessing cognitive function in these patients.

Educational support plays a pivotal role in addressing learning disabilities associated with NF1. Individualized education plans and specialized educational services are essential for accommodating specific learning needs and fostering academic success[1]. Executive functioning deficits, commonly observed in NF1, underscore the importance of tailored educational strategies that enhance working memory and organizational skills, helping patients navigate the demands of schooling and daily life[31]. Academic accommodations, such as extended test-taking time and tutoring support, can further assist students in optimizing their learning potential[2,37,53]. Given the early onset and persistent nature of cognitive and behavioral problems in NF1, regular neuropsychological evaluations are essential. Surveillance should be stratified by age to identify key developmental concerns at different life stages[39,45,46].

Intervention strategies should be stratified based on age to provide targeted support at different developmental stages. In pediatric patients, early identification of ADHD and learning disabilities through standardized assessments is critical, and behavioral therapy remains the primary approach[1,27]. They often require individualized educational plans and specialized support services to accommodate their learning difficulties. Adolescents face unique challenges related to self-identity, peer relationships, and transition into adulthood, requiring psychological interventions and structured vocational support. They might require continued cognitive-behavioral therapy to ad-

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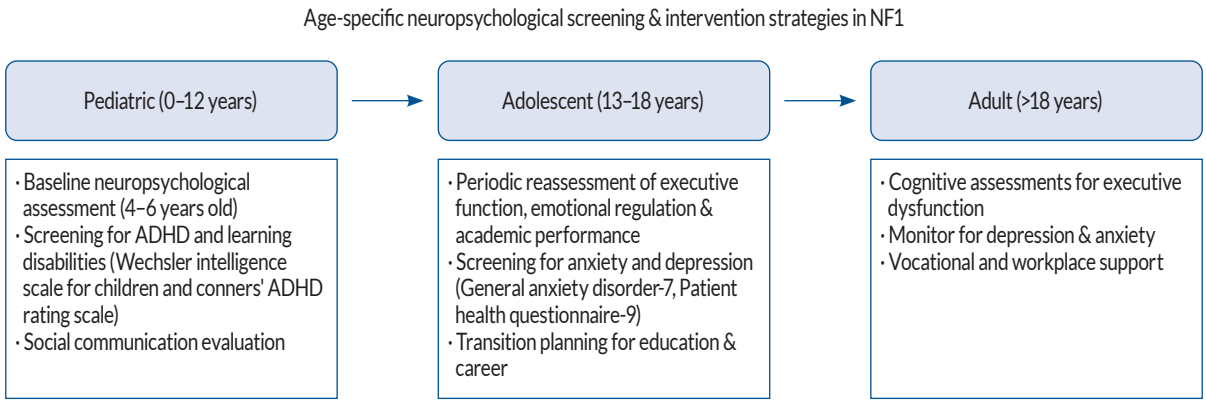

Fig. 5. Suggested age-specific neuropsychological screening & intervention strategies in neurofibromatosis type 1 (NF1). ADHD : attention-deficit hyperactivity disorder.

dress emotional dysregulation and psychiatric symptoms, while career counseling and structured transition programs can facilitate their integration into higher education or employment[35]. In adults, cognitive dysfunction may impact workplace performance and independent living. Therefore, for them, ongoing psychosocial support, workplace accommodations, and vocational rehabilitation are essential to managing executive dysfunction and promoting independent living[45]. Currently, there is no standardized, widely accepted guideline specifically dedicated to neuropsychological screening and intervention for patients with NF1. Fig. 5 outlines a suggested framework for age-specific neuropsychological screening and intervention strategies for NF1 patients, providing a structured approach to cognitive and behavioral management across the lifespan.

While progress has been made in understanding NF1-associated cognitive and behavioral problems, several research gaps remain. The efficacy of MEK inhibitors, initially developed for NF1-related tumors, is being investigated for potential cognitive benefits[23]. Preliminary findings suggest that the use of MEK inhibitors may confer beneficial effects on neurocognitive function[32,56]. Based on individual-level analysis, the study found clinically meaningful improvements in verbal comprehension, processing speed, number sequencing, and motor speed[32]. Additionally, further studies on biomarker identification, such as neuroimaging correlates and genetic modifiers, could refine early diagnosis and personalized interventions. Multicenter trials are also needed to evaluate the long-term impact of behavioral and pharmacological therapies in NF1 populations.

OTHER SYSTEMIC COMPLICATIONS AND THEIR MANAGEMENT

Skeletal abnormalities are a common feature of NF1, with manifestations ranging from scoliosis and tibial dysplasia to osteopenia and short stature. Scoliosis affects up to 30% of NF1 patients, with a subset developing severe, progressive forms that require surgical intervention[55]. Tibial dysplasia, often present at birth, can lead to pseudoarthrosis and significant functional impairment[48]. Additionally, generalized low bone mineral density (BMD) and increased fracture risk have been reported in NF1, likely due to dysregulated RAS/MAPK signaling affecting osteoblast function[14]. To mitigate these complications, early identification through regular clinical assessments, including annual spinal examinations and radiographic evaluations when indicated, is recommended. For patients with suspected osteoporosis, dual-energy X-ray absorptiometry scans should be considered to evaluate BMD[7]. Chronic pain, often arising from bone deformities, scoliosis, or plexiform neurofibromas, further exacerbates physical limitations and psychological distress in NF1 patients. Addressing pain requires a multidisciplinary approach incorporating physical therapy, orthopedic interventions, and pharmacologic pain management strategies, including non-steroidal anti-inflammatory drugs, neuropathic pain medications, and psychological support[35].

Beyond skeletal complications, cardiovascular issues represent another significant health burden in NF1. Hypertension is prevalent, affecting up to 30% of adults with NF1, and may arise from various underlying causes, including renal artery stenosis, PCCs, or primary essential hypertension[20]. NF1-asso-

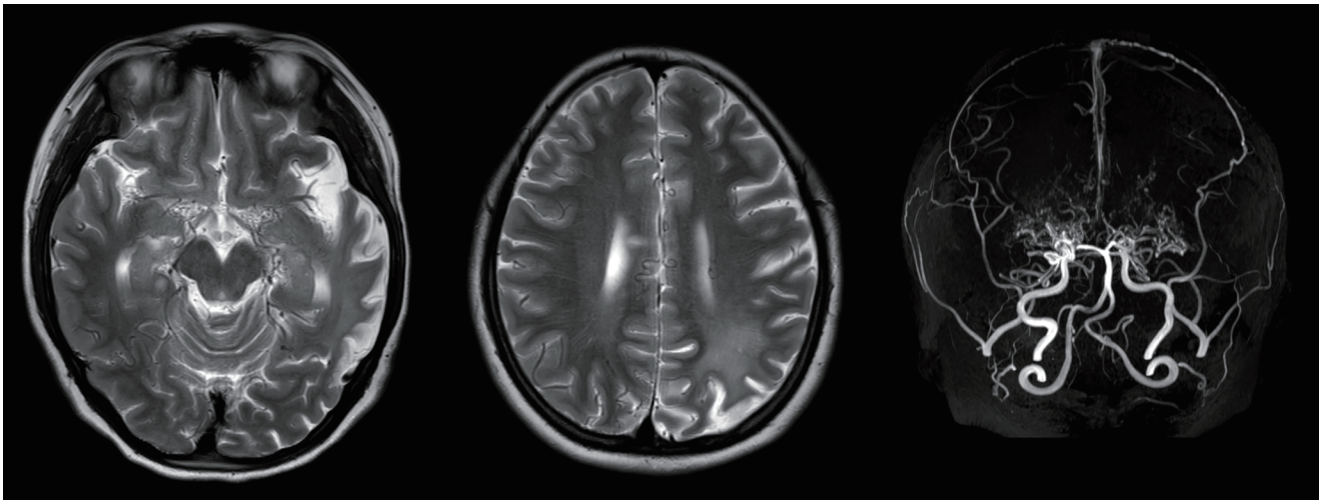

Fig. 6. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) findings in a patient with neurofibromatosis type 1-related moyamoya syndrome. Axial T2-weighted image (left) demonstrates prominent collateral vessels around the basal cistern and basal ganglia. MRA (right) reveals bilateral occlusion of the terminal internal carotid arteries and middle cerebral arteries with extensive collateral formation. T2-weighted MRI (middle) shows geographic hyperintensity involving the left parietotemporal lobe with diminished volume, suggestive of previous ischemic injury.

ciated vasculopathy, characterized by arterial stenosis and aneurysms, can further contribute to life-threatening conditions such as stroke and aortic dissection[40,50]. Renal artery stenosis is one of well-recognized vascular abnormality in pediatric NF1 and often presents with early-onset or treatment-resistant hypertension[40]. Moyamoya syndrome, characterized by progressive stenosis of the intracranial internal carotid arteries and development of compensatory collateral networks, is one of the cerebrovascular manifestations and has been observed patients with NF1 (Fig. 6)[43]. Although there is currently no consensus guideline for vascular screening in NF1, regular blood pressure monitoring is generally advised for NF1 patients, beginning in childhood, with additional assessments such as renal artery imaging or endocrine testing warranted for persistent hypertension. In cases where vasculopathy is suspected, cardiac evaluation using echocardiography and MRI with angiography is recommended to facilitate early diagnosis and intervention[20]. When cerebrovascular disease is suspected, particularly in NF1 patients presenting with sudden-onset neurological deficits, prompt brain imaging is essential. MRI with angiography is useful initial tool, while cerebral angiography remains the gold standard for diagnosing moyamoya syndrome. Diagnostic and therapeutic approaches for moyamoya in NF1 patients follow the same general principles as for non-NF1 patients[43]. Cardiovascular complications not only impair physical function but also increase overall morbidity and mortality risk. Early detection and appropriate management strategies, including antihypertensive therapy, surgical intervention for vascular stenosis, and lifestyle modifications, are essential for optimizing cardiovascular health and improving long-term outcomes[20].

CONCLUSION

NF1 is a lifelong, multisystem disorder that requires continuous surveillance and multidisciplinary care. The condition predisposes patients to various complications, including malignant and benign tumors, cognitive and behavioral impairments, cardiovascular abnormalities, and skeletal deformities. Given the progressive nature of NF1, early detection and proactive management are essential to improving patient outcomes and minimizing morbidity.

A structured, age-specific approach to surveillance is crucial for addressing the evolving needs of NF1 patients. In childhood, routine ophthalmologic assessments aid in the early identification of OPGs, while neurodevelopmental evaluations help manage cognitive and behavioral challenges. Adolescence necessitates ongoing academic support and mental health monitoring, whereas adulthood requires heightened vigilance for malignancies such as breast cancer and MPNSTs, as well as

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cardiovascular complications.

Comprehensive NF1 management relies on a multidisciplinary framework that integrates neurology, oncology, genetics, psychology, and rehabilitation medicine. A patient-centered approach, incorporating genetic counseling, individualized educational plans, and targeted therapies, is fundamental in optimizing quality of life. Through sustained clinical vigilance and coordinated care, the burden of NF1 can be mitigated, ultimately enhancing long-term health outcomes for affected individuals.

AUTHOR'S DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : SC; Data curation : SC; Formal analysis : SC; Funding acquisition : SC; Methodology : SC; Project administration : SC; Visualization : SC; Writing - original draft : SC; Writing - review & editing : SC

Data sharing

None

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