Profile and Outcomes of Neurofibromatosis Type 1 (NF1) Patients in a Tertiary Government Hospital in the Philippines: A Retrospective Descriptive Study

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ABSTRACT

Background. Neurofibromatosis Type 1 (NF1) is a genetic disorder with a wide range of clinical manifestations, including skin changes, behavioral issues, and skeletal deformities. Despite being relatively common, there is a lack of local studies in the Philippines.

Objective. This study aimed to investigate profiles of individuals with NF1 seen at the Philippine General Hospital and their outcomes following various interventions.

Methods. A review of medical records of all patients with confirmed NF1, identified through databases from the Institute of Human Genetics and the Philippine General Hospital from 1999 to 2022, was done. Demographic, clinical, treatment, and outcome data were reviewed and evaluated. Data gathered included clinical profile, interventions, and survival. Additionally, for patients with congenital pseudarthrosis and NF1, radiologic findings, treatments, and functional outcomes such as union maintenance and refracture were evaluated.

Results. The mean age of 50 patients with NF1 at initial evaluation was 10.8 ± 5.5 years, with an average symptom onset at 1.9 ± 3.7 years. Common features included café-au-lait spots (100%), axillary and inguinal freckling (17%), and cutaneous (15%) or plexiform (11%) neurofibromas. Interventions noted included surgery for intracranial tumors and multiple surgeries for congenital pseudarthrosis of the tibia. Six patients with congenital pseudarthrosis of the tibia had a median age of presentation at 0.5 years, with most requiring repeated surgical interventions and receiving bisphosphonate treatment for better bone union outcomes.

Conclusion. A multidisciplinary approach is necessary to address the varied clinical manifestations of NF1, including biological, biomechanical, psychological, and developmental issues. Standardization and adherence to established multidisciplinary protocols are necessary to achieve optimal outcomes.

Keywords: Neurofibromatosis 1, pseudarthrosis, bisphosphonates (diphosphonates)

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INTRODUCTION

Neurofibromatosis Type 1 (NF1) is a multisystemic autosomal dominant disorder characterized by café-au-lait macules, intertriginous freckling, cutaneous fibromas, behavior problems, and learning disability. Less common but potentially serious manifestations include optic nerve and central nervous system gliomas, peripheral nerve sheath tumors, scoliosis, tibial dysplasia, vasculopathy, endocrine and pulmonary disease.[1] It is caused by pathogenic variants in the *NF1* gene, which encodes the tumor suppressor neurofibromin. Loss of neurofibromin function leads to overactivation of the RAS-MAPK pathway, promoting cell proliferation and tumor formation. Mitogen-activated protein kinase (MEK1/MEK2), key kinases in this pathway, activate MAPK, and their overactivation is linked to various tumors.[2] The condition has a wide spectrum of clinical manifestations owing to its complete penetrance and highly variable expression.[3] NF1 is a relatively common genetic disorder with a worldwide prevalence between 1/3000 and 1/4000.[4]

Diagnosis of NF1 is established when, using the 2021 Revised Diagnostic Criteria for NF1, two or more features are fulfilled by an individual without an affected parent or when there is one characteristic feature in an individual with a heterozygous pathogenic mutation in the *NF1* gene, OR with an affected parent.[1,5] The treatment for NF1 is focused on longitudinal multidisciplinary care, focused on age-specific monitoring of clinical manifestations, early recognition, and symptomatic treatment of complications.[4]

The skeletal system is affected in sixty (60) percent of patients with NF1, commonly presenting as tibial dysplasia and spinal deformities. Worsening of deformities is commonly observed without treatment; thus, surgical intervention is often necessary. But due to their rarity and heterogeneous presentation, evidence regarding the best surgical approach is scarce.[6] For tibial dysplasia or pseudarthrosis, fracture union has satisfactory functional results in over 80% of children by doing surgical resection, intramedullary nailing, and bone grafting. Wearing a brace until skeletal maturity is achieved is mandatory to minimize the risk of refracture.[6] Pharmaceutical interventions for tibial pseudarthrosis are generally limited, but documented drugs include bisphosphonates, recombinant bone morphogenetic protein, and lovastatin.[6-8]

At present, there are no known local studies in the Philippines that describe the profile and outcomes of NF1 patients and those with congenital pseudarthrosis having NF1. The Division of Clinical and Metabolic Genetics in PGH, which offers the only fellowship training in genetics in the country, receives referrals for genetic evaluation and counseling of these patients and their families. Some patients are initially referred due to the presence of congenital pseudarthrosis of the tibia and are later assessed to have NF1. In recent years, the Division, together with the Department of Orthopedics, has also started offering bisphosphonate infusion as an adjunct to surgery to those with congenital pseudarthrosis of the tibia. This is to address the high osteoclastic activity associated with this condition, decrease graft and fracture site resorption and increase the success rate and maintenance of union.[4] This study aimed to describe the profile and outcomes of these patients,, after various interventions, to contribute to local NF1 data based on the experience of a single tertiary hospital.

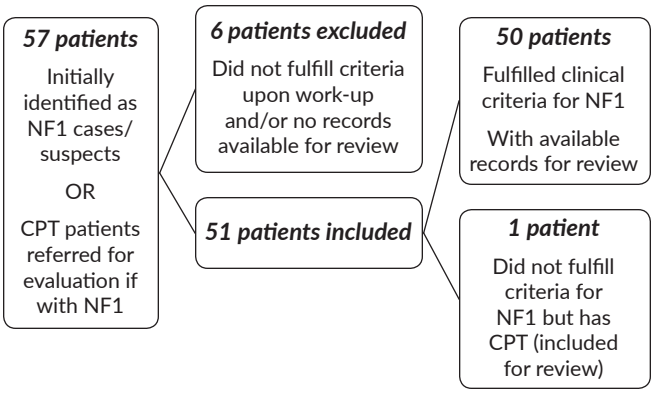

Figure 1. Flow diagram of included/excluded patients based on NF1 criteria and the reasons for exclusion.

METHODS

This is a single-center descriptive study that reviewed medical records of diagnosed NF1 patients from 1999 until 2022. The patients included in the study were those diagnosed with NF1, fulfilling the updated 2021 clinical criteria (Table 1).

Patients with NF1 were identified from the patient databases of the Institute of Human Genetics (IHG), Clinical Genetics Unit - NIH, and Division of Clinical and Metabolic Genetics, Department of Pediatrics - PGH. Records were reviewed, and those not meeting the updated diagnostic criteria were excluded. The number of patients included and excluded in the study is shown in Figure 1.

Information on demographics, socioeconomics, clinical characteristics, family history, relevant diagnostic workups (biochemical, radiologic, etc.), interventions (medical and surgical), and outcomes (functional score, maintenance of union, refracture) were collected and recorded. The following study outcomes were obtained:

A. For NF1 patients – (1) Demographic and clinical profile, (2) Medical and surgical interventions, (3) Clinical outcomes
B. For patients with Congenital Pseudarthrosis of the Tibia and NF1 – (1) Radiologic findings, (2) Medical and orthopedic interventions, (3) Outcomes including functional score, maintenance of union, and re-fracture

Source documents included medical records accessed from the PGH Records Section and the Clinical Genetics

Table 1. Revised Diagnostic Criteria for Neurofibromatosis Type 1 [5]

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if ***two or more*** of the following are present: • Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals [a] • Freckling in the axillary or inguinal region [a] • Two or more neurofibromas of any type or one plexiform neurofibroma • Optic pathway glioma • Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging • A distinctive osseous lesion such as sphenoid dysplasia, [b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone • A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue, such as white blood cells
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

[a] *If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1, but exceptionally, the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.*

[b] *Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.*

Table 2. Crawford Classification of Congenital Pseudarthrosis of the Tibia [9]

Type I	Anterior bowing with a preserved medullary canal and cortical thickening at the apex of the deformity; good prognosis
Type II	Presence of thinned medullary canal, cortical thickening, and trabeculation defect
Type III	Cystic lesion, which may be fractured; patients have fractures at an early age and require early treatment
Type IV	There is a frank pseudarthrosis with atrophic ends of the tibia

Unit of NIH. The use of records complied with the Data Privacy Act of 2012. Necessary institutional permits for access to medical records (paper charts and online records) were secured prior to data collection. Conduct of the study complied with the rules set forth by the University of the Philippines Manila Research Ethics Board approval (UPMREB 2023-0671-0).

For the sources of bias in a retrospective descriptive study, there may be a selection bias due to the non-random selection of subjects, and when certain patients were systematically excluded due to the targeted inclusion of patients with NF1. Information bias may arise from inaccurate or inconsistent recording of variables in medical records. Recall bias may be encountered when subjects with the disease may remember or report past exposures or variables differently.

Table 3. Boyd Classification of Congenital Pseudarthrosis of the Tibia [10]

Type I	Anterior bowing
Type II	Pseudarthrosis with hourglass constriction
Type III	Pseudarthrosis with bony cyst
Type IV	Pseudarthrosis with sclerotic fracture segments
Type V	Presence of a complementary dysplastic fibula
Type VI	Intraosseous lesion (neurofibroma or schwannoma)

Table 4. Paley Classification of Congenital Pseudarthrosis of the Tibia [11]

Type I	Bowed tibia and fibula, but no fractures
Type IIA	Bowed but not fractured tibia, with a fibular fracture at the lateral malleolus at the station
Type IIB	Bowed but not fractured tibia, with a fibular fracture with proximal migration of the lateral malleolus
Type III	Fractured tibia, with a bowed but not fractured fibula
Type IVA	Fractured tibia and fibula, with lateral malleolus at station
Type IVB	Fractured tibia and fibula, with proximal migration of the lateral malleolus
Type IVC	Fractured tibia and fibula, with a bone defect of the tibia and proximal migration of the lateral malleolus

There may be detection bias if outcomes of interest cannot be ascertained well, and there was variation in how the data were recorded by the reviewers. This can be addressed by having one or two consistent researchers (principal investigator and secondary investigator) to do the evaluation of records. Any uncertainty in the variables to be recorded was discussed and decided upon by the two reviewers.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables, and mean and standard deviation (SD) for normally distributed continuous variables.

For those with congenital pseudarthrosis of the tibia, radiographic morphologic classifications used in this study were: Crawford, Boyd, and Paley.[9-11] The more commonly used Crawford Classification (1986) highlights the degree of dysplasia (Table 2), while the Boyd Classification (1982) includes any presence of fibular pseudarthrosis or any intraosseous lesion of the tibia, such as a neurofibroma (Table 3).[10] The Paley Classification (2019), like the Boyd, recognizes the complementary fibula pseudarthrosis, but also considers whether there is proximal fibular migration or not, which has implications on ankle stability (Table 4).[11]

The ASAMI (Association of the Study and Methods of Ilizarov) functional score (Table 5) was obtained for the patients with Congenital Pseudarthrosis of the Tibia who underwent orthopedic surgical management.[12]

Table 5. ASAMI Functional Score [12]

Excellent	Active, no limp, minimum stiffness (loss of <15deg knee extension / <15deg dorsiflexion of the ankle), no reflex sympathetic dystrophy (RSD), insignificant pain
Good	Active, with one or two of the following: limp, RSD, significant pain
Fair	Active, with three or all of the following: limp, stiffness, RSD, significant pain
Poor	Inactive (unemployment or inability to perform daily activities because of injury)
Failure	Amputation

RESULTS

There were 50 patients diagnosed with NF1 based on clinical criteria from 1999 to 2022. No patients underwent genetic testing. Among the diagnosed cases, there were 22 (44%) females and 28 (56%) males. Except for an adopted individual with unknown ethnicity, all the patients are of Filipino descent (49/50, 98%). The majority of the patients came from the National Capital Region (24/50, 48%) and from Southern Luzon (17/50, 34%).

The mean age of the patients upon consultation at the Genetics Clinic was 10.8 years old (SD ± 5.5). The mean age of onset of symptoms was 1.9 years (SD ± 3.7). All patients presented with café au lait spots or macules at first consult; 20 patients (60%) had them at birth. Eighteen patients (36%) had axillary freckling only, two patients (4%) had inguinal freckling only, and 17 (34%) had both. Fifteen patients (30%) had cutaneous neurofibroma, while 11 (22%) had plexiform neurofibroma, which were found at the temporo-orbital area, orbit, face (with extension to the parasellar region), cheek, shoulder, chest, mediastinum, and in the anterior neck extending to the nape, back, and groin. Six (12%) patients had congenital pseudarthrosis of the tibia ± fibula. Two (4%) patients had sphenoid bone dysplasia (Table 6).

Thirteen (13) patients continued to have consultations with the Genetics service until 2022, with the oldest being 20 years of age, while most patients were lost to follow-up.

Eight (8) patients underwent surgical interventions. One (1) patient had excision of an intracranial tumor (pilocytic astrocytoma WHO Grade 1). One (1) patient had anterior orbitotomy, debulking of mass, lateral canthopexy, and tarsorrhaphy on the left eye due to an orbital plexiform neurofibroma. Five (5) patients underwent excision of congenital pseudarthrosis of the tibia and fibula. One (1) patient had an outright below-knee amputation because of the clinical severity on presentation (2 apex deformity and pseudarthrosis of the tibia). Five (5) patients underwent Ilizarov reconstruction, of these four (4) had repeat Ilizarov reconstructions due to refracture, and two (2) had secondary surgeries for debridement, repeat bone grafting, and revisions of the Ilizarov fixator for fractures or dislocations in other adjacent areas. Three (3) of these patients had medical intervention, specifically pamidronate infusion, after Ilizarov surgery.

Table 6. Clinical Profile of Neurofibromatosis Type 1 Patients Seen at the Philippine General Hospital from 1999 to 2022 (n = 50)

	Mean	SD
Age of onset of symptoms (years)	1.9	± 3.7
Age of patient first seen at Genetics Clinic (years)	10.8	± 5.5
	No. of Cases (Percentage, %)	
Family History		
Had 1st degree relatives with NF1 (based on history and physical examination)	16 (32)	
No data available	4 (8)	
Clinical characteristics (based on NF1 criteria)		
Café-au-lait spots	50 (100)	
Intertriginous freckling		
Axillary freckling only	18 (36)	
Inguinal freckling only	2 (4)	
Both	17 (34)	
Cutaneous neurofibroma	15 (30)	
Plexiform neurofibroma	11 (22)	
Lisch nodules	12 (24)	
Long bone dysplasia/Congenital pseudarthrosis	6 (12)	
Sphenoid bone dysplasia	2 (4)	
Other associated clinical features with NF1		
Cranial tumors (pilocytic astrocytoma)	1 (2)	
Seizures/ Epilepsy	6 (12)	
Scoliosis	10 (20)	
Learning/behavior issues	3 (6)	
Global Developmental Delay or Intellectual disability	6 (12)	

There were six (6) NF1 patients who had congenital pseudarthrosis of the tibia and fibula (Table 7). The median age at presentation was 0.5 years, while they were diagnosed at a median age of 4 years. Five (5) patients had involvement of the left leg. Three (3) patients had a Crawford III classification, having non-atrophic tibial pseudarthroses. The other three (3) patients had a Crawford IV with atrophic tibia and fibula pseudarthroses. Three (3) patients originally had Paley II with bent but intact tibia and a dysplastic distal fibula fracture, two (2) of which had proximal fibular migration on presentation. The other three (3) patients presented with Paley IV with both tibia and fibula with atrophic fracture ends, one (1) of which had fibular proximal migration on presentation. Three (3) patients underwent bisphosphonate infusion with pamidronate at 1 mg/kg/dose as a priming dose, then 1.5 mg/kg/dose every 2 months on subsequent infusions.

Among the six (6) patients who underwent orthopedic surgical procedures for the CPT, two had excellent, one had good, one had a poor outcome, and one had failure of Ilizarov reconstruction leading to amputation (knee disarticulation).

Table 7. Clinical Profile of Patients with NF1 and Congenital Pseudarthrosis of the Long Bones and their Outcomes (n = 6)

Patient No.	Sex	Present age	Age at presentation	Age at diagnosis	Laterality	Congenital Pseudarthrosis of the Tibia (CPT) Classification	Radiologic findings	ASAMI functional score	Refracture	Maintenance of Union (years)	Intervention
1	M	22	Birth	4	Left	Crawford IV, Boyd V, Paley IVA	Distal tibia and fibula pseudarthrosis, with no proximal migration of fibula	Good	1	5	Ilizarov Surgery (2006, 2014)
2	F	19	5	19	Left	Crawford IV, Boyd V, Paley IVA	Distal tibia and fibula pseudarthrosis, with no proximal migration of fibula	Excellent	1	8	Ilizarov Surgery (2009, 2017)
3	M	10	Birth	4	Left	Crawford III, Boyd V, Paley IIA	Originally, a Paley IIA with a bent but intact tibia and dysplastic fibula pseudarthrosis before fracturing Preoperatively, a Crawford III with non-atrophic ends of the tibia pseudarthrosis → Converted to a Crawford IV during Ilizarov treatment due to the massive resorption Distal tibia and fibula pseudarthrosis, posterior knee subluxation, secondary femur osteopenia	Failure	2 proximal tibia distal femur *not at the original pseudarthrosis site	N/A	Ilizarov Surgery (2019) With secondary procedures (x3) for pin site infections, fracturing or dislocating at other sites during Ilizarov treatment Pamidronate 1.5 mkdose (2x in 1 year) Eventually underwent Knee Disarticulation (2021)
4	F	9	1	1	Right	Crawford IV, Boyd V, Paley IVB	Severe 2 apex deformity and pseudarthrosis of the tibia with dysplastic fibula pseudarthrosis and proximal migration	N/A (patient did not undergo Ilizarov reconstruction) Now walking with a below-knee prosthesis	N/A	N/A	Below-knee amputation (2023)
5	M	8	Birth	4	Left	Crawford III, Boyd V, Paley IIB	Originally, a Paley IIB with bent but intact tibia and dysplastic fibula pseudarthrosis Preoperatively, a Crawford III with non-atrophic ends of the tibia pseudarthrosis → Converted to a Crawford IV during Ilizarov treatment due to massive resorption Distal tibia and fibula pseudarthrosis, distal femur fracture secondary to disuse femur osteopenia The patient also has knee instability post-Ilizarov removal	Poor	2 (*2nd refracture not at original pseudarthrosis site)	2	Ilizarov Surgery (2020, 2023) With secondary procedures (x2) for repeat bone grafting, fracturing at other sites For the fabrication of a hinged knee-ankle-foot clamshell orthosis Pamidronate 1.5mkdose
6	F	6	1	2	Left	Crawford III, Boyd V, Paley IIB	Originally, a Paley IIB with a bent but intact tibia and dysplastic fibula pseudarthrosis with proximal migration Preoperatively, a Crawford III with non-atrophic ends of the tibia pseudarthrosis	Excellent	0	3 years	Ilizarov Surgery (2020) Pamidronate 1-1.5mkdose

DISCUSSION

NF1 is a genetic disorder caused by pathogenic variants in the *NF1* gene encoding for the tumor suppressor protein *neurofibromin,* which regulates the Ras signaling pathway. This condition manifests with multiple tumors on nerve tissues, including the brain, spinal cord, and peripheral nerves, but it may initially be recognized by café au lait spots in a child.

This study included 50 unrelated patients who fulfilled the clinical criteria without molecular genetic testing. Among these patients, only 32% had a first-degree relative with NF1, which is lower than previously reported.[13,14] The most common clinical feature on diagnosis in our cohort was café au lait spots, which is similar to other studies.[3,15] While the mean age of initial presentation of symptoms was noted to be at 1.9 years old, the mean age when first evaluated at the Genetics Clinic was 10.8 years old, with the youngest patient seen at three years of age. Efforts to improve awareness among both medical workers and the public are critical for early detection. Early recognition and diagnosis of affected individuals ideally lead to better monitoring and minimization of serious medical complications.[16]

In this study, 12 patients were also noted to have Lisch nodules. Lisch nodules usually do not interfere with vision, hence it does not warrant significant medical intervention. The utility of the detection of Lisch nodules is mainly in confirming the diagnosis of NF1, and they are often observed in older affected individuals.[17]

In our cohort of patients, spinal deformities such as scoliosis were found in 20% of patients, while congenital pseudarthrosis was seen in 12% (6 out of 50) of patients. This data is consistent with several studies where tibial dysplasia is the second most common osseous manifestation in NF1 after spinal deformities.[5]

Bowing deformity and pseudarthrosis are seen in 5.7 percent of the long bones, of which the tibia is most frequently involved.[18] Similarly, among the six patients in our cohort who had pseudarthrosis, the majority had involvement of the tibia (71%). The exact reason for the involvement of the tibia in NF1 is unknown. Since some histologic studies of pseudoarthrosis showed a thick cuff of hamartomatous tissue surrounding the pseudarthrosis, hypotheses suggest that cells from the hamartoma may not undergo osteoblastic differentiation and may have high osteoclastic activity.[5,19]

Eighty percent (80%) of patients with CPT were identified in previous studies to carry pathogenic variants of the NF1 gene. Biallelic NF1 inactivation in tissues is documented in some NF1-CPT patients.[20] A higher proportion of *de novo* mutation carriers manifests with bone fractures compared to those with inherited variants.[5] In our setting, diagnosis is mostly based on clinical features and/or family history. Genotypic characterization for this cohort is not available due to limited funds for genetic testing, which is mainly an out-of-pocket expense. Molecular profiling may help in correlating genotypes with CPT phenotypes and their response to treatment (i.e., presence of CPT, risk of fractures/refractures, response to bisphosphonates, etc.).

The Ilizarov Limb Fixation and Reconstruction (ILFR) Service of the Department of Orthopedics has been reconstructing Congenital Pseudarthrosis of the Tibia since the 1990s; however, the outcomes were dismal with a 100% refracture rate. Maintenance of the union has been difficult due to the non-adherence to bracing after Ilizarov removal and the lack of uniformity with regard to the procedures being done, together with the application of the Ilizarov fixator.

In an effort to improve the maintenance of union, the ILFR has recently been overhauling its surgical protocol to include a combination of aggressive resection of the deceased periosteum of the tibia and fibula, intramedullary rodding, application of Ilizarov, and cross union using auto- and allografts. Together with the Division of Clinical Genetics, it has also started addressing the hyper-resorptive state of the condition, by giving pamidronate infusions after surgery to reduce graft resorption, and to effect and maintain union. Bisphosphonate therapy (e.g., pamidronate and zoledronic acid) may be helpful in preserving the bone morphogenetic protein (BMP) 7-induced formation by the inhibition of osteoclastic bone loss. Important factors that lead to union in CPT may include sufficient fixation, meticulous resection of dysplastic tissue, and the net anabolic environment for bone healing.[6]

Confounding variables that may affect outcomes in our patients with CPT include the heterogeneity in clinical severity of the presentations, the varying adherence to follow-ups and pamidronate infusions, and the maintenance of post-Ilizarov bracing. It is currently too early to conclude or give recommendations regarding the optimal treatment protocol from the current small study population. It is prudent, however, to continue combining the techniques mentioned, including the bisphosphonate infusions, as larger studies, particularly that of Paley, have had success with these combinations.[11] Standardization and adherence to the current protocols must be established and continued until skeletal maturity.

Several patients in our cohort also presented with plexiform neurofibromas (11 out of 50, 22%). Until recently, management of plexiform neurofibromas was limited to surgical resection and often resulted in recurrence. However, new drugs have recently been approved for NF1 with plexiform neurofibroma. The MEK1/MEK2 inhibitor selumetinib has demonstrated encouraging efficacy in pediatric patients with NF1 and symptomatic, inoperable plexiform neurofibromas. In a Phase I/II clinical trial, approximately 70% of children experienced a measurable reduction in tumor volume. This tumor shrinkage was also associated with meaningful improvements in patient-reported outcomes, including reduced tumor-related pain, enhanced quality of life, increased strength, and improved range of motion.[21] Mirdametinib, another MEK1/MEK2 inhibitor, has recently been approved by the FDA for NF1 with plexiform neurofibromas.[22] With these new developments in the management of NF1, the

importance of patient registries cannot be overemphasized. Patient registries serve as a valuable resource for bringing together individuals with rare diseases from around the world to participate in research studies.[23]

Genetic counseling of families with NF1 is also of utmost importance. Around 50% of individuals with NF1 have an affected parent, while 50% have the disorder as a result of a *de novo* NF1 pathogenic variant. A child of an individual with NF1 has a 50% chance of inheriting the condition due to its autosomal dominant manner of inheritance. Penetrance is close to 100%; thus, an offspring who inherits an NF1 pathogenic variant will be expected to develop features of NF1, but these features may be less severe or more pronounced in an affected child than in the affected parent. For a proband with NF1 with no apparent family history, recommended evaluation of the parents includes history and physical examination with particular attention to dermatologic lesions, ophthalmologic examination, skeletal deformities, and behavioral or learning issues. A negative family history cannot totally rule out NF1 in the family members unless parents and siblings have undergone detailed clinical examination for signs of NF1. Parental somatic and germline mosaicism may also be a possibility.[1]

Limitations of the Study

Retrospective descriptive studies may have selection, information, and ascertainment bias that may affect the interpretation and analysis of data. Missing data may also be a challenge. In this study, imputation methods were not employed as the data collected were mostly qualitative. Reasons for missing data in a retrospective study include incomplete information in the medical records.

CONCLUSION

The achievement of better outcomes in the treatment of Neurofibromatosis type 1 involves its early detection and its associated conditions, the employment of a multidisciplinary team to address the biological, biomechanical, psychological, and developmental implications of the condition, and the standardization and adherence to established multidisciplinary protocols until skeletal maturity. The current teams are still building on strategies to achieve optimal outcomes for these patients.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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