Epidemiology and Outcomes of Neurofibromatosis Type 1 (NF-1): Multicenter Tertiary Experience

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Purpose: The aim of this manuscript was to assess the epidemiology and clinical features of Neurofibromatosis type 1 (NF-1) based on the newly published revised NF-1 diagnostic criteria and to evaluate complications of NF-1 including neurodevelopmental disorders.

Patients and methods: A retrospective cross-sectional observational study was conducted in the Ministry of National Guard Health Affairs (MNGHA) healthcare organization branches including four tertiary hospitals and 51 primary health care centers in different regions in Saudi Arabia. This study included all patients diagnosed with NF1 using the revised NIH diagnostic criteria published in 2021 that were registered at the electronic medical records (EMR) from 2015 to 2021.

Results: A total of 184 patients fulfilled the diagnostic criteria and were included in this study. The median age at diagnosis was 11 years (IQR: 4.00–20.25). The most encountered diagnostic criteria in this study were Café-au-lait macules (85.3%), and (42.9%) were found to have two or more neurofibromas with plexiform neurofibroma being the most common subtype (23.36%), approximately (36.4%) of the patient with optic pathway glioma. Nearby (26.6%) of the patients displayed different type of tumors. Iris Lisch nodules were presented in 36.4% of patients at a median age of 12 years (IQR: 9.0–21.8). Cardiovascular abnormality was encountered in 9.8% of the patients. Around 27.7% of the patients reported headache and 11.4% of the patient suffered from different type of epilepsy. Besides, 10.5% of the patients had intellectual disability, 33.8% suffered from communication disorders, and 4.9% patients had ADHD.

Conclusion: The results of this study will enable practitioners to adopt a more holistic approach and prioritize numerous attributes, which they can subsequently incorporate into their therapeutic methodologies. Furthermore, the identification of these attributes will facilitate an expeditious and accurate diagnosis. Hence, the implementation of intervention during its nascent phase may result in a more advantageous consequence.

Keywords: neurofibromatosis type 1, café-au-lait macule, glioma, neurofibromas

Introduction

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen’s disease, is a hereditary condition that impacts various bodily systems and presents with a notable tendency to develop tumors, along with associated neurological and cutaneous symptoms. This condition has an incidence of 1 in 2000 to 3000 individuals in the general population, regardless of gender or ethnicity, and is typically inherited in an autosomal dominant manner. The germline mutation of NF 1 is
situated on chromosome 17q11.2, specifically inside the region responsible for encoding a protein known as neurofibromin. This protein exerts a crucial influence on the regulation of the RAS signaling pathway by inhibiting cell growth. Consequently, the absence of this gene that inhibits growth results in a noticeable rise in cell division stimulation. It is important to mention that a second somatic mutation is necessary to eliminate the heterozygosity of the NF1 gene.\textsuperscript{1,5,6}

The National Institutes of Health (NIH) have established a clear set of criteria for diagnosing NF-1. Although the NIH criteria have been established, many papers in the literature contend that modifications are necessary for the pediatric population to ensure the criteria’s reliability as a diagnostic tool. A study involving 1893 NF-1 patients below the age of 21 revealed that 46% of sporadic NF-1 cases below the age of 1 did not satisfy the diagnostic criteria established by the NIH. However, almost all NF-1 children met these criteria by the age of 8 years.\textsuperscript{7} Undoubtedly, molecular genetic testing has the potential to address these diagnostic challenges in pediatric patients with atypical symptoms who do not fulfill the criteria set by the NIH.\textsuperscript{8} In addition, a group of international experts in the field of NF-1 collaborated on a study with the goal of refining the diagnostic criteria for NF-1 to improve the accuracy of diagnoses. The study proposed the inclusion of genetic testing as a component of the diagnostic criteria, alongside newly identified phenotypic characteristics.\textsuperscript{9}

The Clinical Care Advisory Board of the National Neurofibromatosis Foundation, now known as the Children’s Tumor Foundation, conducted a formal evaluation of the NIH NF-1 criteria. However, no changes or modifications were suggested. Nevertheless, the clinicians’ adherence to the preposition and the objective of enhancing the NIH criteria has not been retracted yet. This occurs because the application of NIH criteria may lead to an erroneous clinical diagnosis of NF-1 for Legius syndrome (LGSS).\textsuperscript{10} On 2021, a paper was published discussing updated diagnostic criteria for NF-1 and LGSS, incorporating several revisions. The revised diagnostic criteria were specifically designed to achieve maximal consensus among clinicians, thereby striking a balance between sensitivity and specificity, in contrast to the prior criteria.

The updated diagnostic criteria for NF-1 specify that a minimum of two of the following criteria must be present in order to confirm the diagnosis.\textsuperscript{11} The Café au lait macules are one of the skin characteristics commonly observed in individuals with NF-1, and they are typically the initial feature to be recognized. The criteria specified that the macules should be six or more and have a diameter of at least 5 mm in pre-pubertal age, and a diameter of at least 15 mm in post-pubertal patients.\textsuperscript{12} The additional cutaneous characteristic is the existence of freckles in the axillary or inguinal regions.\textsuperscript{11} The presence of two or more neurofibromas or one plexiform neurofibroma is another prominent feature. Additionally, the presence of two or more Lisch nodules, which are melanocytic iris hamartomas, can be detected through slit lamp examinations or the identification of two or more choroidal abnormalities. These abnormalities manifest as bright, patchy nodules that can be visualized using optical coherence tomography (OCT) or near-infrared reflectance (NIR) imaging. Optic pathway gliomas (OGP) have diverse manifestations, varying from absence of symptoms to visual acuity impairment, contingent upon their specific location. In addition, there are specific bone abnormalities such as sphenoid wing dysplasia, anterolateral bowing of the tibia, or pseudoarthrosis of a long bone. A heterozygous pathogenic NF-1 variant with a variant allele fraction of 50% is present in apparently normal tissue, indicating a genetic condition. However, a child who has a parent diagnosed with NF-1 merely needs to meet one or more of the criteria mentioned above in order to receive a diagnosis.\textsuperscript{10}

Published research indicated that people with NF-1 experience higher rates of illness and death compared to the general population.\textsuperscript{13,14} In order to improve one’s quality of life and decrease the occurrence of illness and death, it is important to effectively address and manage the difficulties related with NF-1. In addition to the neuro-oncological effects, vasculopathy is a recognized complication linked to NF-1. This includes conditions such as pulmonary stenosis, cerebral and renal artery stenosis, moyamoya disease, hypertension, and an elevated risk of strokes.\textsuperscript{15-17} Moreover, individuals with NF1 exhibit elevated frequencies of experiencing seizures. The systematic study findings indicate that the lifelong prevalence of epilepsy in NF-1 patients is 5.4\%.\textsuperscript{18} Furthermore, a regional investigation carried out at King Saud University Medical City in Riyadh, Saudi Arabia revealed that 21.1% of a group of 50 individuals with NF 1 who were under the age of 18 experienced epilepsy.\textsuperscript{19} NF-1 can also impact the skeletal system, leading to widespread abnormalities such as reduced bone density (osteopenia), below-average height (short stature), and abnormally large head size (macrocephaly).\textsuperscript{20}

Mutations in the NF-1 gene can lead to a range of clinical neuropsychiatric symptoms observed in individuals with NF-1. Despite being partially comprehended; NF-1 is strongly linked to various neurodevelopmental diseases. The
Diagnostic and Statistical Manual fifth edition (DSM-5) categorizes these conditions as intellectual disability, communication disorders, learning disorders, motor disorders, attention-deficit-hyperactive disorder (ADHD), autism spectrum disorder (ASD), and disruptive behavioral disorders.

Insufficient data exists in Saudi Arabia about the clinical characteristics and sequelae, such as neurodevelopmental abnormalities, associated with NF-1. A comprehensive descriptive study was required to have a better understanding of the disease’s characteristics among both juvenile and adult populations due to the absence of thorough examinations. Hence, the aim of this study was to evaluate the epidemiological and clinical characteristics of NF-1 using the recently published updated diagnostic NF-1 criteria, as well as the associated consequences including neurodevelopmental disorders.

**Methods**

**Study Design**

This is a retrospective observational cross-sectional study that was conducted in all campuses of the Ministry of National Guard Health Affairs (MNGHA) healthcare organization scattered in different regions in Saudi Arabia (Riyadh, Jeddah, Al-Ahsa, Dammam, and Medina.). Data about epidemiology and outcomes of diagnosed neurofibromatosis type 1 disease adult and pediatric patients of both genders were collected. In addition, clinical presentation and comorbidity associated with NF-1 patients were assessed.

**Data Extraction**

Data were accessed through BESTCare 2.0A system, which is a MNGHA medical record system designed to store medical history records electronically. Chart review method was used by the research team members to collect the data using a special data collection form. Patients were given serial numbers and their data were filled and stored in a Microsoft Excel sheet. All recorded cases that are registered at BESTCare system from April 2015 to April 2021 who are diagnosed with NF-1 using revised NIH diagnostic criteria for NF-1 by Genetics in Medicine 2021 (GIM) were included. Patients with neurofibromatosis type 2 or Legius syndrome and other different variants were excluded. The data collection sheet was divided into three sections. The first section was for demographic data (gender, age, and age at diagnosis). The second part contains features and complications of the disease. In this study, patients were considered to be short in stature when the height is below the tenth percentile for the patient’s age. An IQ below 70 was considered an intellectual disability. Patients who had to attend special schools, failed in school multiple times, or were previously diagnosed by a neuropsychologist were considered with learning disability. Furthermore, patients whose blood pressure was above the 95th percentile for their age were considered hypertensive.

**Statistical Analysis**

Statistical Package for the Social Sciences software SPSS (release 27.0.1, IBM Corp, Armonk, NY) was used for data analysis. Descriptive statistics were reported as frequencies and percentages for categorical data. Median and inter-quartile range (IQR) were used to present continuous variables as they were non-normally distributed.

**Results**

This study was conducted on 184 Saudi pediatric and adult patients 86 (46.7%) males and 98 (53.3%) females diagnosed with neurofibromatosis type-1 disease and their ages ranged from three to 76 years with a median of 16 years (IQR: 9.00–16.00). They were diagnosed at a median age of 11 years (IQR: 4.00–20.25) and were last seen at a median age of 15 years (IQR: 9.00–24.00). The studied patients were followed up for a median duration of five years (IQR: 3.00–6.00). All 184 patients fulfilled the revised NIH diagnostic criteria for NF-1, with an average of three positive diagnostic criteria per patient.

**NF-1 Revised Criteria**

The results for the revised NIH diagnostic criteria observed in this study are shown in Table 1. Most of the included patients 157 (85.3%) presented with Cafe-au-lait macules (CALMs) at a median age of 8 years (IQR: 3.0–16.0), 64
(34.8%) had skin fold freckling of whom 48 (26.1%) had axillary freckling, which was the most common observed type, 1.1% had inguinal, 5.4% had both, and 2.2% had unspecified type of skin fold freckling.

Additionally, neurofibromas were observed in 79 (42.9%) of patients, including cutaneous neurofibromas, plexiform neurofibromas 22 (12%), 43 (23.4%), respectively, and eight (4.3%) had both, with plexiform neurofibromas being the most dominant subtype. A total of 28 patients of those with plexiform neurofibroma required surgical intervention, only one received chemotherapy and another one required both treatment modalities. Moreover, Iris Lisch nodules were presented in 36.4% of patients at a median age of 12 years (IQR: 9.0–21.8). A total of 12 (6.5%) of the patient had distinctive osseous lesion at a median age of four years old (IQR: 1.5–10.5), of whom, seven (3.8%) had sphenoid wing dysplasia, two (1.1%) had anterolateral bowing of tibia and three (1.6%) had pseudarthrosis of a long bone. Optic nerve glioma was seen in 38 (20.7%) of patients 16 (8.7%) of them had associated visual impairment, 12 (6.5%) had chiasm involvement, seven (3.8%) had their orbital nerve affected and one (0.5%) had optic atrophy, at a median age of eight years old (IQR: 4.0–13.0). Moreover, two patients required surgical intervention, another two required chemotherapies and one patient received radiotherapy, but 33 (17.9%) of them required no intervention. Furthermore, around fifth of the patients (23.5%) had a parent with NF1 in which 79.1% had affected fathers and 20.9% had mothers with NF-1.
NF-1 Associated Comorbidities

Table 2 presents signs and symptoms of NF-1 other than those included in diagnostic criteria of NIH and significant comorbidity associated with development of the disease. In this study, cardiovascular abnormality was encountered in 18 (9.8%) of whom 12 (6.5%) were hypertensive, three (1.6%) had congenital heart disease, two (1.1%) had renal or cerebral artery stenosis and one (0.5%) had moyamoya disease. In addition, 26 (14.1%) of the patients presented with congenital or idiopathic scoliosis and 17 (9.2%) have short stature. Besides, 27 (14.7%) of the patients were found to have macrocephaly. Leg length discrepancy was found in five (2.7%), whereas four (2.2%) had precocious puberty. Another reported symptom was headache in 51 (27.7%), this study revealed that 21 (11.4%) of the patients had epilepsy with different seizure types and this include (focal motor seizures in six (3.3%), generalized motor tonic–colonic seizures in seven (3.8%) and eight (4.3%) had unspecified type of seizures) at a median age of the seizure onset of 10 years (IQR: 5.0–16.0). Regarding treatment, six (28.6%) were started on carbamazepine, five (23.8%) were controlled on levetiracetam and one (4.8%) started on phenytoin. While only three (14.3%) had drug-resistant epilepsy.

In terms of neurofibrosarcoma, it was identified in two (1.1%) patients, one of them required surgery. Neuro-imaging identified different types of tumors and the analysis showed that malignant brain tumor was detected in 21 (11.4%) of patients some of which had hamartoma 11 (6%), glioma was observed in five (2.7%), while schwannoma in two (1.1%)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Frequency</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Cardiovascular abnormalities</td>
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</tr>
<tr>
<td>Scoliosis</td>
<td>26</td>
<td>14.1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>21</td>
<td>11.4</td>
</tr>
<tr>
<td>Tumors</td>
<td>49</td>
<td>26.6</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Malignant brain tumor</td>
<td>21</td>
<td>11.4</td>
</tr>
<tr>
<td>Glioma</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Astrocytoma</td>
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<td>0.5</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>11</td>
<td>6.0</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.1</td>
</tr>
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<td>Extra-neural tumors</td>
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<td>14.1</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>76.9</td>
</tr>
<tr>
<td>Short stature</td>
<td>17</td>
<td>9.2</td>
</tr>
<tr>
<td>Macrocephaly/ Hydrocephalus</td>
<td>26</td>
<td>14.1</td>
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<tr>
<td>Leg length discrepancy</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Headache</td>
<td>51</td>
<td>27.7</td>
</tr>
</tbody>
</table>
and astrocytoma in only one (0.5%), of whom, two (1.1%) required surgery. Extra-neuronal tumors were detected in 26 (14.1%); which involved breast cancers in four (2.2%), gastrointestinal stromal tumors, and phaeochromocytoma, each in one (0.5%), of whom, seven (3.8%) required surgery and only one (0.5%) received chemotherapy.

Neurodevelopmental Disorders

Table 3 presents neurodevelopmental disorders that developed among the study participants. A total of 67 pediatric patients developed neurodevelopmental disorders with an age ranging from 0 to 14 years. According to the (DSM-5) classification division of neurodevelopmental disorders, the study found that seven (10.5%) of the patients had intellectual disability, 23 (33.8%) suffered from communication disorders, which include speech sound disorder, language disorder, childhood onset fluency disorder, social communication disorder, unspecified communication disorder. In addition, 10 (14.9%) patients had ADHD, two (3.0%) patients had ASD, 14 (20.9%) patients had learning disorders, nine (13.4%) patients had motor disorders, and six (13.4%) patients had disruptive behavioral disorders. Other neuropsychological disorders findings included, seven (10.5%) of patients experienced anxiety, three (4.5%) patients displayed agitation, irritability, and violence. Lastly, four (6.0%) patients had self-injury behavior, suicide ideation, depression, and anorexia.

Discussion

This study evaluated the revised diagnostic criteria, neuroradiological features, and both the associated physical and psychiatric comorbidities of NF1. All patients included in the study met the criteria for NF1 diagnosis with a mean of three criteria per patient, and their ages ranged from 3 to 76 years with a median of 16 years (IQR: 9.00–16.00). A comprehensive comprehension of the epidemiology and consequences of NF-1 is fundamental in order to deliver optimum healthcare and enhance the quality of life for those impacted.

NF-1 Revised Criteria

Café Au Lait Macules

In this study, café-au-lait macules have been observed to be the most prevalent cardinal criteria reaching 157 (85.3%) of all patients. Café-au-lait macules are flat tan-brown skin pigmentationsthat can be found in different areas of the body which increase in size and quantity with age. Like other global and local studies, In addition, it is the first dermatological

<table>
<thead>
<tr>
<th>Neurodevelopmental Disorders (N=67)</th>
<th>N</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual Disability</td>
<td>7</td>
<td>10.5</td>
</tr>
<tr>
<td>Communication Disorders</td>
<td>23</td>
<td>33.8</td>
</tr>
<tr>
<td>ADHD</td>
<td>10</td>
<td>14.9</td>
</tr>
<tr>
<td>ASD</td>
<td>2</td>
<td>3.00</td>
</tr>
<tr>
<td>Learning Disorders</td>
<td>14</td>
<td>20.9</td>
</tr>
<tr>
<td>Motor Disorders</td>
<td>9</td>
<td>13.4</td>
</tr>
<tr>
<td>Disruptive Behavioral Disorders</td>
<td>6</td>
<td>9.0</td>
</tr>
<tr>
<td>Other psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>10.5</td>
</tr>
<tr>
<td>Agitation, Irritability, Violence</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Others (ex. Self-injury, Suicide ideation, Depression, Anorexia)</td>
<td>4</td>
<td>6.0</td>
</tr>
</tbody>
</table>
manifestation that can be distinguished at an early age by clinicians and patients. Leading to a deeper investigation of the pathology behind those abnormal patches which ultimately lead to investigating the possibility of NF-1 diagnosis.

**Skin-Fold Freckling**
In this study, skin-fold freckling was seen in 34.8%, which was similar to the findings of a previous local study, but comparatively another local study found a much lower incidence of 27.5%. They can manifest on areas of the skin that are not exposed to sunlight. Freckles commonly appear in the axilla and inguinal regions. The occurrence of freckling gradually develops, therefore, it may not be seen in very young children with NF1.

**Iris Lisch Nodules**
In our study, Iris Lisch nodules were not as prevalent as CALMs, reaching up to 67 patients (36.4%) which other studies have found similar frequencies of 42.0% and 33.5%. Unlike CALMs, Iris Lisch nodules are one of the most suggestive and disease specific sign of NF-1. Irish Lisch nodules are innocuous iris hematomas that can be seen in a slit lamp examination. They are usually present in all adults and nearly half of children younger than five-year age. Lisch nodules are known to be age dependent. They manifest in almost all patients with NF-1 over the age of 30; conversely, they are unusual to present before the age of two; which explains the median age in this study being 12 years (IQR: 9.0–21.8).

**Neurofibroma**
In this study, there were 79 patients with neurofibromas of both forms which counts for 42.9%. One previous local study has found that plexiform fibromas counted for 19.4% and cutaneous neurofibromas counted for 20.6%. While another local study found that plexiform neurofibromas count for 24.0% but did not specifically mention cutaneous neurofibromas.

This study has found that solitary plexiform neurofibromas were found in 23.4%, solitary cutaneous neurofibromas were found in 12.5%, coexistence of both were found in 4.3%, and unspecified neurofibromas were found in 3.3%. This could be due to the increase of technological diagnostic and screening investigating modalities that could help in discovering the existence of deeper plexiform neurofibromas compared to the superficial cutaneous neurofibromas that could be recognized clinically or even by the patients.

Therefore, early diagnosis can further help the prognosis of these neurofibromas especially by allowing surgical excision to be an option of intervention. The occurrence of these neurofibromas typically rare before early childhood, however, the occurrence is known to be relatively high among patient with NF-1.

**Optic Nerve Glioma**
In this study, the prevalence rate of OPGs was 20.7%; which is relatively lower than one local study with prevalence of 34%. This could be due to the inclusivity of adults along with the pediatric sample in the study. It’s the most common type of brain tumor manifesting in NF-1. Mostly seen in children younger than seven years of age with estimated prevalence range of 10–15%. This study found a median presenting age of eight years old (IQR: 4.0–13.0).

These tumors are either symptomatic that manifest as visual impairment, loss of visual acuity, proptosis, strabismus or incidentally found during the routine MRI/CT.

**Distinctive Osseous Lesions**
In this study, distinctive osseous lesions were found in 6.5%, and included sphenoid wing dysplasia, pseudoarthrosis of a long bone, and anterolateral bowing of tibia. They usually are the result of the mass effect caused by neurofibromas leading to bone deformities that are commonly located in the tibia and fibula. As a consequence of this bone remodeling, anterolateral tibial bowing, pseudoarthrosis, and fractures can be developed. Due to the lack of direct clear evidence, further studies should be done to confirm this association.

A local study mentioned that distinctive osseous lesions were found in one patient that is described as thinning of the long bone cortex with or without pseudoarthrosis. Furthermore, another local study revealed skeletal involvement to count up to 16.8%, yet the type or nature of these involvements was not specified or explained. Sphenoid wing dysplasia is the asymmetrical hypoplasia of the greater wing of the sphenoid bone that might extend to the proximate structures such as the temporal and the occipital bones. So, it can be noticed by clinicians by the facial asymmetry. It is the most distinguishing skull abnormality of NF-1 patients, that was found in 7 patients in this study.
NF-1 Associated Comorbidities

Cardiovascular Abnormalities

In this study, we found relatively higher incidence of cardiovascular abnormality reaching 9.8%. This was lower than the findings of a previous local study that found that the incidence of cardiac diseases to be 6.1%. Upon specifying, 6.5% had hypertension, 1.6% had congenital heart diseases, 1.1% had renal or cerebral artery stenosis, and 0.5% had moyamoya disease. Multiple studies have demonstrated the presence of cardiac complications in individuals with NF1, such as valvular pulmonary stenosis, peripheral pulmonary stenosis in the branches, abnormalities in the atrial and ventricular septa, aortic coarctation (both thoracic and abdominal), and hypertrophic cardiomyopathy. According to a recent study conducted by Lin et al, the prevalence rate of cardiovascular problems in individuals with NF1 is rather low, specifically 2.3%. Nevertheless, in a separate investigation, Lama et al documented cardiac abnormalities in 18.8% of individuals diagnosed with NF1.

Scoliosis

In our study, the prevalence rate of scoliosis was found 14.1%, which is almost half (27.3%) of the findings of a previous study and reasonably higher (10.6%) than the finding of another study. Scoliosis is the predominant skeletal abnormality reported in NF1. Evidently, male individuals with NF1 are more frequently impacted by scoliosis in comparison to the idiopathic scoliosis population. The progression of dystrophic scoliosis varies from non-dystrophic scoliosis, with a greater likelihood of requiring corrective surgery. However, it should be noted that non-dystrophic scoliosis in NF1 does not consistently show positive results when treated with bracing. Consequently, it is imperative for all individuals with NF1 to undergo a careful and systematic monitoring process conducted by a skilled team. This is necessary to promptly identify the progression of spinal curves and enhance the effectiveness of treatment plans, ultimately leading to improved results and increased patient adherence.

Epilepsy

In this study the prevalence rate of epilepsy was found to be 11.4% (n = 21), whereas other studies found higher incidence of 16.9% and 21.2%. In our study, of those 21 patients, 6 patients (28.6%) had focal motor seizures, seven patients (33.3%) had generalized motor tonic–colonic seizures, and eight patients (38.1%) had unspecified seizure. NF1 patients have been found to have a higher likelihood of developing epilepsy over their lifetime, with prevalence rates ranging from 4% to 14%. Cerebral vasculopathies and hydrocephalus are predisposing conditions that increase the likelihood of seizures.

Short Stature

In our study, the prevalence rate of short stature to be 9.2%, while the only two local studies suggested higher prevalence rates of 18.1% and 15%, respectively. According to an article published by NIH, the average height of those with NF-1 is relatively lower than the general population. Prior research on short stature in NF1 has indicated that 13–33% of individuals with the condition showed a height below the anticipated range. Although the exact cause of short stature in children with NF1 has not been fully understood, research conducted on genetically engineered mice strains with Nf1 gene mutations has shown that the inactivation of the Nf1 gene mostly affects bone and somatic growth. The investigations have shown that mice with genetically modified strains that do not express Nf1 in their bones exhibit skeletal defects.

Macrocephaly or Hydrocephalus

In this study, we found that around 14.7% of the patient developed macrocephaly with or without hydrocephalus. Nevertheless, no other local studies have investigated this specific complication. Hydrocephalus in NF1 can be caused by tumors, hamartomas, and other developmental diseases that disrupt the circulation or absorption of cerebrospinal fluid (CSF). Large bilateral vestibular schwannomas and other brain tumors associated with NF2 can cause hydrocephalus by constricting or blocking the passageways through which CSF flows. As that this study encountered the death of one patient due to this fatal complication, it is encouraged to do further research about its association with NF-1. Hence, attracting attention of physicians for immediate recognition and improved management.
Leg Length Discrepancy
In our study, leg length discrepancy was seen in only five patients (2.7%), which is similar to that of previous studies.\textsuperscript{19,22} Individuals with tibial dysplasia have an increased vulnerability to fractures and are at risk of developing pseudarthrosis, a condition characterized by poor healing of the fractured tibia.\textsuperscript{37} Tibial dysplasia may lead to a condition known as limb length discrepancy, characterized by one leg being longer than the other. Some individuals with NF1 may experience overgrowth of one leg, resulting in increased size and length, even in the absence of any underlying skeletal abnormalities.\textsuperscript{37} The underlying factor in these instances is the excessive proliferation of the soft tissues of the limb.\textsuperscript{37}

Precocious Puberty
In our study, there were four (2.2%) patients that had precocious puberty. Other local studies have found similar frequencies.\textsuperscript{19,22} Precocious puberty could be associated with optic chiasm tumors. The pathophysiology behind it is likely to be due to the anatomical locations.\textsuperscript{11} The prevalence of this disorder in individuals with NF1 is 3%, which is significantly more than the prevalence of approximately 0.6% observed in the general population.\textsuperscript{21} Central precocious puberty has been predominantly observed in children with NF1 who also have OPG. This finding aligns with the hypothesis that lesions in proximity to the hypothalamus disrupt the regulatory function of the central nervous system in inhibiting the hypothalamic-pituitary-gonadal axis, leading to the early initiation of puberty.\textsuperscript{21}

Headache
In our study, 27.7% of the patients suffered from headache and this frequency was significantly higher than that of previous studies with prevalence rate of 15.2% and 16.9%.\textsuperscript{19,22} Most of the neurological pathologies that originate in the brain cause headache as very unspecific symptom. Due to the fact that NF-1 is a neurological disease that mainly affect the nerve some of which are anatomically located in the cranium for example OPGs and other brain masses and has a lot of neurological complication such as epilepsy and hydrocephalus, it is very typical of such symptom to be of that prevalence.

Neurodevelopmental Disorders
In this study, neurodevelopmental disorders were investigated due to their significant importance in impacting the patients’ quality of life as well as their caregivers. Neurodevelopmental disorders are a large group of disorders that occur during the ongoing development period and usually start manifesting in childhood. According to DSM-V, this group of disorders include intellectual disabilities, communication disorders, ASD, ADHD, learning disorders, motor disorders, disruptive behavior disorders.

Upon reviewing the local articles published about NF1 and its psychiatric complications, only two have touched upon the surface of this matter. One of which has only studied the frequency of intellectual and learning disabilities.\textsuperscript{19} However, they failed to assess other neurodevelopmental disorders like communication disorders and autism spectrum disorders. While another has discussed the fact that NF1 phenotype was linked with cognitive decline.\textsuperscript{22} They drew this questionable conclusion of the existence of an association without providing the evidence or data that supports; their claim in their results section or clarifying the base on which their statement stands through their analysis.

Intellectual Disabilities
In this study, the prevalence of intellectual disability has reached 10.5% of all NF-1 pediatric patients which is not only higher than the general population but also higher than what the global study have found. In a local study, the prevalence was 18.1% which higher than the mentioned global study and this study.\textsuperscript{19} Intellectual disability, previously known as mental retardation, defined as an IQ of equal to or lower than 70. It is considered the leading cognitive impairment that is observed in NF-1 patients. A large global study has estimated the prevalence of intellectual disability among NF-1 patients to be from 4% to 8% which is relatively higher than the general population (3%).\textsuperscript{38} This could theoretically be due to the amount of radiation and chemotherapy those patients are exposed to regularly and from an early age resulting in a physiological alteration in the brain leading to this intellectual impairment.\textsuperscript{38}
Communication Disorders
In this study, around 33.8% of the pediatric NF-patients found to have communication disorders which is triple of that is in the general population. Communication disorders are disorders that result in deficits in language, speech, and communication. There are five communication disorders in the DSM-5: Language Disorder, Speech Sound Disorder (previously Phonological Disorder), Childhood-Onset Fluency Disorder (Stuttering), Social (Pragmatic) Communication Disorder, and Unspecified Communication Disorder (dsm5). According to the DSM-V, communication disorders are estimated to have a prevalence of 5% to 10%.

Attention Deficit Hyperactivity Disorders/ Autism Spectrum Disorders
The findings of this study reported that 10 patients (14.9%) have ADHD while two patients (3.0%) have ASD. The only other local study mentioned that ADHD was observed in a couple of patients but did not mention the specific percentage. Furthermore, they identified 15 patients to have cognitive impairments of any sort but did not specify ASD despite concluding a link between the phenotype of NF1 with social cognition deficits and ADHD. Between thirty and fifty percent of children diagnosed with NF1 exhibit behavioral issues characterized by attention impairments, hyperactivity, and impulsivity, which meet the diagnostic criteria for ADHD as outlined in the DSM-IV.

Learning Disorders
In this study, around 20.9% of all patients had some sort of learning disability and poor school performance, some of which were registered in special schools due to that. A local study found very low incidence of 6.1% comparably. Even so a study has elaborated on that almost 75% of NF-1 patients need school accommodation and remedial reaching. In a previous study of neurodevelopmental disorders in NF-1 population, it was found that almost 20% of NF-1 patients had learning disability which was double of that in general pediatric population.

NF-1 can also significantly impair the quality of life of patients, highlighting the criticality of comprehensive care and support services. A comprehensive comprehension of the epidemiology and consequences of NF-1 is critical for physicians in practice, given the significant ramifications it has on patient care, prognosis, and the allocation of healthcare resources. Consequently, physicians must possess a comprehensive understanding of its epidemiology in order to promptly identify and diagnose cases. Prompt detection enables opportune implementation of interventions, such as genetic counseling and monitoring for complications including optic pathway gliomas, neurofibromas, and skeletal abnormalities. Furthermore, an examination of NF-1 outcomes yields significant knowledge regarding the pathogenesis of the ailment and facilitates the prognostication of disease advancement and complications. This data is crucial for the formulation of individualized treatment strategies and the establishment of practical anticipations for patients and their families. Furthermore, the comprehensive epidemiology and consequences of NF-1 makes a valuable contribution to continuous research endeavors that seek to enhance diagnostic techniques, treatment alternatives, and overall patient outcomes. Practicing physicians can enhance patient care, improve clinical outcomes, and contribute to the progression of medical knowledge in this domain through proper analysis of the epidemiology and consequences of NF-1.

Conclusion
This study focused on analyzing the clinical features, concomitant medical conditions, and neuroimaging findings of NF1. The results will enable physicians to take a more holistic approach and pay special attention to certain features that might be utilized in their therapeutic practices. Identifying these characteristics will help with a fast and precise diagnosis. Thus, introducing intervention in a premature phase can result in a more favorable outcome.

Data and Materials Availability
All data are available from the corresponding author on reasonable request.

Ethical Approval
This study was approved by the institutional review board at King Abdullah International Medical Research Center (KAIMRC), and the identifying number of the IRB approval was IRB/1507/22. Informed consent was obtained from all
subjects involved in the study. The study was designed and conducted in accordance with the ethical principles that have their origin and comply with the Declaration of Helsinki. Parent or legal guardian of patients under 18 years of age provided informed consent.

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References


