



The First Documented Iraqi Case of Jean de Grouchy Syndrome

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Abstract

Background: Jean De Grouchy syndrome (18p deletion syndrome; partial monosomy 18p) is a chromosomal disorder associated with variable developmental, intellectual, dysmorphic, and neurological manifestations. Since its original description in 1963, the reported phenotype has expanded considerably. Recognition of rare chromosomal disorders remains particularly important in populations that are underrepresented in the medical literature.

Objective: To document the first identified Iraqi case of Jean de Grouchy syndrome (18p deletion syndrome) and to characterize the patient's clinical, developmental, dysmorphological, cytogenetic, and neuroimaging findings.

Patients and Methods: A 13-year-old boy was evaluated because of significant developmental and intellectual impairment and characteristic dysmorphic facial features.

A detailed clinical assessment included developmental and adaptive functioning, speech and language abilities, motor skills, behavior, and dysmorphological examination. Developmental history was obtained from the parents. Cytogenetic analysis was performed because of the combination of intellectual disability, developmental delay, and dysmorphic features. Non-contrast Computed Tomography (CT) of the brain was also performed to evaluate neurological manifestations and exclude major structural intracranial abnormalities.

Results: The patient was born to non-consanguineous parents with no reported family history of a similar disorder or known chromosomal abnormality. He demonstrated marked global developmental and adaptive impairment, severe expressive language limitation, impaired comprehension, poor adaptive skills, and dependence on others for several activities of daily living. Fine and gross motor difficulties and behavioral abnormalities were also reported.

Dysmorphological examination demonstrated a relatively long and narrow face, prominent and relatively high nasal bridge with an elongated nose, mildly down-slanting palpebral fissures, relatively large prominent ears, a mildly prominent chin and lower facial profile, and an open-mouth appearance with a prominent or everted lower lip.

Chromosome analysis demonstrated a 46, XY karyotype with deletion of the short arm of chromosome 18 (18p-), establishing the diagnosis of 18p deletion syndrome. Brain CT demonstrated mild generalized cerebral/cortical volume loss, somewhat more prominent in the temporal regions, with mild associated ventricular prominence and no acute intracranial abnormality.

Conclusion: This report documents a clinically recognizable case of Jean de Grouchy syndrome (18p deletion syndrome) in Iraq. The combination of significant developmental and intellectual impairment, characteristic dysmorphic features, conventional cytogenetic confirmation of 46, XY, 18p-, and associated mild cerebral volume loss supported the diagnosis.

To our knowledge, this appears to be the first documented Iraqi case of Jean de Grouchy syndrome reported in the medical literature. The case highlights the value of careful clinical phenotyping, cytogenetic investigation, and neuroimaging in the recognition and documentation of rare chromosomal disorders.

Keywords: Jean de Grouchy Syndrome; Iraq; Rare Disorders

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Introduction

In 1963, the French geneticist Jean de Grouchy (Figure 1) and his colleagues published a landmark paper that provided the very first description of 18p- syndrome (also known as Monosomy 18p).

They documented a case involving a complex mix of physical anomalies and intellectual disability occurring in association with partial autosomal deletion [1].

The recognition of de Grouchy syndrome emerged during the formative years of human cytogenetics, when chromosomal deletions were beginning to be recognized as causes of recognizable patterns of congenital anomalies and developmental impairment. The syndrome is associated with deletion of the short arm of chromosome 18, now commonly designated 18p deletion syndrome or monosomy 18p [1-8].

The early 1960s represented an important period in medical genetics. Chromosome abnormalities were increasingly being used as what Weiss and Mayeda called natural “experiments of nature.” Deletions were particularly valuable because the loss of a chromosomal segment could potentially reveal the location and function of genes carried in that region.

By 1969, several deletion syndromes had already become recognizable including the relatively well-defined Cri du chat syndrome, resulting from deletion of the short arm of chromosome 5.

It was within this developing cytogenetic framework that the first cases of what came to be associated with de Grouchy syndrome were identified.

In 1969, Weiss and Mayeda noted that, unlike the later cases, the de Grouchy patient did not have the short stature that became a recurring feature in the subsequent series.

Thus, from the beginning, phenotypic variability was part of the history of the syndrome.

Following the original 1963 report, several investigators independently described additional patients with deletion of the short arm of chromosome 18. The year 1964 was therefore an important period in establishing that the original observation represented a recurring chromosomal disorder rather than an isolated anomaly.

In 1964, Van Dyke, Valdmann, and Mann reported Probable deletion of the short arm of chromosome 18.

Their observations helped establish several features that would recur in subsequent cases. Weiss and Mayeda specifically mention

the resemblance of Van Dyke's patients to individuals with Turner syndrome.

Several patients in this early series also had webbing of the neck, an observation that was repeated in later cases, including the Weiss and Mayeda patient.

This Turner-like appearance was historically significant because it demonstrates how clinicians initially approached these patients through comparison with better-known chromosomal syndromes.

Another important 1964 publication was that of Bühler, Bühler, and Stalder, entitled: Partial monosomy 18 and anomaly of thyroxine synthesis.

The report illustrates another characteristic of early chromosome-deletion research: investigators were not simply documenting physical abnormalities but were also attempting to determine whether the chromosomal defect was associated with specific biochemical or physiological abnormalities.

Also in 1964, R. L. Summit reported deletion of the short arms of chromosome 18.

Together, the reports appearing in 1964 strengthened the evidence that deletion involving the short arm of chromosome 18 produced a recognizable clinical pattern.

According to Weiss and Mayeda's later synthesis, short stature and intellectual impairment became particularly consistent findings among the cases reported after de Grouchy.

By the middle of the 1960s, the accumulated cases began to reveal a recognizable pattern. Weiss and Mayeda emphasized three broad categories:

Growth abnormality

Almost all of the patients reported after the original de Grouchy case were described as having short stature.

Intellectual and developmental impairment

Mental retardation, particularly involving verbal abilities, was another recurring observation. The authors specifically note that the impairment was often more pronounced in verbal scores.

Dysmorphic and skeletal abnormalities

The cases showed considerable variation in craniofacial appearance and skeletal development. Webbed neck, abnormal extremities, and changes ranging from clinodactyly to micromelia were reported.

The next major development came from the work of Uchida, McRae, Wang, and Ray, published in 1965 under the title: Familial short arm deficiency of chromosome 18 concomitant with arhinencephaly and alopecia congenita.

This case was particularly important because it expanded the recognized phenotype beyond growth and intellectual impairment to include major developmental abnormalities of the brain and midline structures. Uchida's patient had cebocephaly associated with deletion of the short arms of chromosome 18.

Faint and Lewis reported a case of the syndrome associated with a cyclops malformation.

These observations suggested that chromosome-18 deletion could be associated with a spectrum of severe developmental abnormalities



Figure 1: Jean de Grouchy (1926-2003), A French Geneticist.

involving the forebrain and craniofacial midline.

The early reports gradually revealed an especially striking spectrum of abnormalities including:

- Hypotelorism
- Anencephaly
- Cebocephaly
- Cyclops

This was an important conceptual development. The investigators were beginning to understand that deletion of chromosome 18p did not necessarily produce one uniform phenotype. Instead, the same cytogenetic abnormality could be associated with manifestations of markedly different severity.

Weiss and Mayeda proposed that some of this variation might result from the uncovering of deleterious recessive genes following deletion of one chromosomal copy, a mechanism that Uchida had suggested earlier. This hypothesis is historically significant because it represents an early attempt to explain genotype-phenotype variability at a time when the molecular content of chromosomes was largely unknown.

By 1968, the accumulating evidence had made the association between chromosome-18 deletion and severe craniofacial/brain malformations increasingly apparent.

Gorlin, Yunis, and Anderson reported the association of short arm deletion of chromosome 18 with cebocephaly.

The case reinforced the association between 18p deletion and cebocephaly, an important component of the developing spectrum of midline developmental abnormalities.

In the same period, McDermott and colleagues reported the association of arrhinencephaly with a deficiency involving chromosome 18.

Together, these reports helped establish that the phenotype could include severe developmental abnormalities of the forebrain and craniofacial midline.

The 1969 case reported by Weiss and Mayeda can be regarded as an important early synthesis of the emerging syndrome.

Their patient was a 37-month-old boy referred because of short stature and mental retardation. A provisional diagnosis of "male Turner's syndrome" had initially been made.

The child demonstrated substantial developmental delay. He had delayed motor milestones, could understand simple commands but could not speak, and was functioning developmentally below his chronological age.

His physical examination revealed multiple abnormalities, including:

- Prominent, low-set ears
- High arched palate
- Bilateral pterygium colli
- Small, laterally positioned nipples
- Hypotonia

Hyperextensible joints

Bilateral clinodactyly

Abnormal positioning and relative shortening of the second toes.

Cytogenetic examination demonstrated the characteristic abnormality: 46, XY, 18p-. The abnormal chromosome was present in all 25 metaphases examined, and the investigators interpreted it as a deletion of the short arm of chromosome 18.

The historical importance of the Weiss and Mayeda paper lies in its comparison of the newly reported patient with the earlier cases.

They listed the patients reported by:

- de Grouchy et al. (1963)
- Van Dyke et al. (1964)
- Bühler et al. (1964)
- Summit (1964)
- Uchida *et al.*, (1965)
- Migeon (1966)
- Gorlin, Yunis & Anderson (1968)
- McDermott *et al.*, (1968).

Their synthesis demonstrated that the phenotype was both recognizable and highly variable.

The recurring abnormalities included short stature, intellectual impairment, webbed neck, craniofacial abnormalities, and limb abnormalities. At the same time, severe abnormalities of brain development could occur in some patients, ranging from relatively subtle craniofacial differences to anencephaly, cebocephaly, and cyclops.

This combination of recurring characteristics and striking variability became a defining feature of the early understanding of the syndrome.

The early history of de Grouchy syndrome was not limited to clinical description. The chromosome deletion was also being used as an opportunity to investigate gene localization.

Weiss and Mayeda examined blood-group inheritance in their patient and family. Their patient was heterozygous for the A and B ABO alleles, despite carrying the 18p deletion. Consequently, they concluded that the ABO locus was not located on the deleted short arm of chromosome 18. They similarly concluded that the Rh and MN loci were not located in that region.

This reflects the broader scientific importance of the early deletion cases: chromosome abnormalities were being used not only to diagnose disease but also to construct the first maps of human genes.

The early cases of de Grouchy syndrome illustrate a fundamental transition in medical genetics.

Initially, the 1963 report represented an unusual chromosomal observation. Subsequent reports transformed it into a recognizable syndrome. Each case added another component:

de Grouchy (1963)

→ first recognition of the chromosome-18 deletion

Van Dyke, Bühler, Summit (1964)

→ additional cases, growth impairment, intellectual impairment, Turner-like characteristics and neck abnormalities

Uchida (1965)

→ familial disease and severe brain/midline developmental abnormalities

Migeon (1966)

→ further phenotypic variability and resemblance to other chromosomal syndromes

Gorlin and McDermott (1968)

→ further documentation of cebocephaly and arrhinencephaly

Weiss & Mayeda (1969)

→ systematic comparison of the accumulating cases and an explicit attempt to define the clinical spectrum.

The early documented cases of de Grouchy syndrome occupy an important place in the history of clinical cytogenetics. The original 1963 report by de Grouchy and colleagues established the association between a chromosomal deletion and a complex developmental phenotype. The cases reported during the following five years progressively demonstrated that deletion of the short arm of chromosome 18 could produce a broad spectrum of abnormalities [1-3].

We have previously reported an uncountable number of the first described disorders in Iraq [9-88]. Here, we describe the first documented case of Jean De Grouchy syndrome in Iraq.

Patients and Methods

A 13-year-old boy was evaluated because of significant mental retardation and developmental impairment and characteristic dysmorphic facial features. He was born to non-consanguineous parents, and there was no reported family history of a similar condition or known chromosomal disorder.

A detailed clinical assessment was performed, including evaluation of developmental and adaptive functioning, speech and language abilities, motor skills, behavior, and physical and dysmorphological features.

Developmental history was obtained from the parents. The boy had marked impairment in expressive language and could speak only a few words. He had difficulty understanding and following simple commands and demonstrated poor adaptive skills. He was able to eat with a spoon but had difficulty using it appropriately, could not independently wash his hands, and required assistance with toileting.

He had difficulty holding a pen and was unable to copy a circle. He also had difficulty climbing stairs. Behavioral abnormalities were reported by the family.

On physical examination, particular attention was given to craniofacial morphology, external ears, oral features, neck, extremities, musculoskeletal findings, and genitalia. The external genitalia were normal. The parents were not consanguineous.

Because of the combination of intellectual disability, developmental delay, and characteristic dysmorphic features, cytogenetic investigation was performed. Chromosome analysis

demonstrated a male karyotype with deletion involving the short arm of chromosome 18, consistent with 46, XY, 18p-. The available genetic result was interpreted in conjunction with the clinical phenotype.

A non-contrast Computed Tomography (CT) scan of the brain was also performed to evaluate the neurological manifestations and exclude a major structural intracranial abnormality.

Results

Clinical and developmental findings

The patient demonstrated significant global developmental and adaptive impairment. His expressive speech was markedly limited to a few words, and he had difficulty understanding simple commands. His adaptive functioning was substantially impaired, with dependence on others for several activities of daily living, including personal hygiene and toileting.

Fine motor function was impaired. He had difficulty holding a pen and was unable to copy a simple geometric figure such as a circle. Gross motor difficulties were also present, particularly difficulty climbing stairs. Behavioral abnormalities were reported.

The dysmorphological examination (Figure 2) demonstrated a recognizable craniofacial phenotype characterized by:

- a relatively long and narrow facial appearance;
- a prominent and relatively high nasal bridge with a prominent, somewhat elongated nose;
- mildly down-slanting palpebral fissures;
- relatively large and prominent external ears;
- a mildly prominent chin and lower facial profile; and
- an open-mouth appearance with a relatively prominent or everted lower lip.

The external genitalia were normal. No parental consanguinity was reported.

Cytogenetic findings

Chromosome analysis demonstrated a 46, XY male karyotype with deletion of the short arm of chromosome 18 (18p-). This cytogenetic abnormality established the diagnosis of 18p deletion syndrome (18p- syndrome/partial monosomy 18p) (Figure 2A-2C).

Brain CT findings

Non-contrast CT of the brain (Figure 3A-3C) demonstrated mild generalized cerebral volume loss, characterized by mild prominence of the cortical sulci and cerebrospinal fluid spaces. The prominence



Figure 2A: Facial appearance of the 13-year-old boy demonstrating the characteristic dysmorphic facial features.



Figure 2B: Facial appearance of the 13-year-old boy demonstrating the characteristic dysmorphic facial features.



Figure 2C: Facial appearance of the 13-year-old boy demonstrating the characteristic dysmorphic facial features.

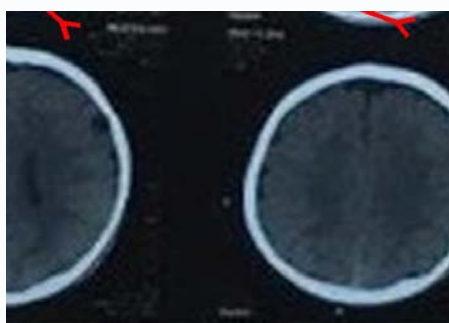


Figure 3A: Axial non-contrast CT image demonstrating mild prominence of the cortical sulci.

was somewhat greater in the temporal regions. There was also mild prominence of the ventricular system, considered likely secondary to the cerebral volume loss.

No focal intracranial mass lesion, acute intracranial hemorrhage, obvious acute territorial infarction, significant midline shift, or mass effect was identified. The basal cisterns were maintained, and the posterior fossa structures were grossly unremarkable. No obvious acute calvarial abnormality was identified.

The CT findings were therefore interpreted as:

1. Mild generalized cerebral/cortical volume loss, relatively more prominent in the temporal regions.
2. Mild associated ventricular prominence.
3. No acute intracranial abnormality.

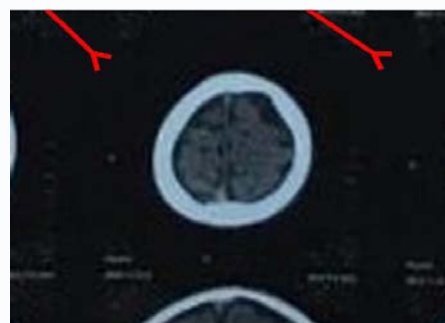


Figure 3B: Axial non-contrast CT image demonstrating mild prominence of the lateral ventricular system and cerebrospinal fluid spaces, consistent with mild cerebral volume loss.



Figure 3C: Coronal non-contrast CT image demonstrating mild prominence of the cortical sulci and cerebrospinal fluid spaces, consistent with mild cerebral/cortical volume loss.

Discussion

Since the first description of 18p deletion syndrome by de Grouchy and colleagues in 1963, an increasing number of affected individuals have been reported worldwide.

Earlier clinical reviews documented more than 150 affected individuals, and subsequent publications have continued to report more than 150 cases worldwide.

More recent literature reviews have referred to more than 300 reported cases. However, the precise number of individuals described in the literature is difficult to determine because published reports have used different inclusion criteria and because many individuals diagnosed with 18p deletion syndrome may not have been reported as individual case reports [4-6].

The present patient represents a clinically recognizable example of 18p deletion syndrome. He is a 13-year-old boy with marked developmental and intellectual impairment, severe expressive language limitation, impaired comprehension of simple commands, poor adaptive skills, and substantial dependence on others for activities of daily living. His developmental profile is consistent with the neurodevelopmental phenotype repeatedly described in individuals with 18p deletion syndrome. Mental retardation and speech or language impairment is among the most characteristic manifestations of the disorder, although their severity varies considerably among affected individuals [1-6].

The facial phenotype in our patient is also compatible with the broad dysmorphic spectrum of 18p deletion syndrome. He had a relatively long and narrow face, prominent/high nasal bridge with an elongated nose, mildly down-slanting palpebral fissures, relatively prominent external ears, a mildly prominent chin and lower facial

profile, and an open-mouth appearance with a prominent/everted lower lip.

Facial dysmorphism is a frequent but variable feature of 18p deletion syndrome, and the absence of a single pathognomonic facial appearance makes recognition dependent on the combination of developmental impairment, dysmorphism, growth characteristics, and cytogenetic findings [1-8].

The cytogenetic finding of 46, XY, 18p- provided the definitive diagnostic basis in our patient. It is important to distinguish this conventional cytogenetic finding from a molecularly defined microdeletion.

In the present case, the available result demonstrates deletion of the short arm of chromosome 18 but does not, by itself, establish the precise genomic size or breakpoint of the deletion. Studies using chromosomal microarray and other molecular techniques have demonstrated substantial variation in deletion size and breakpoint location, helping to explain at least some of the phenotypic variability observed among affected individuals [1-6].

Neuroimaging in our patient demonstrated mild generalized cerebral/cortical volume loss, somewhat more apparent in the temporal regions, with mild prominence of the cerebral ventricles that was considered likely secondary to the volume loss. No mass lesion, hemorrhage, acute infarction, midline shift, or other acute intracranial abnormality was identified.

Neurological abnormalities and structural brain abnormalities have been reported in 18p deletion syndrome, with the most severe abnormalities occurring in a subset of patients with larger or particular deletions [3-6].

The relatively mild cerebral volume loss observed in our patient therefore represents a potentially relevant neuroimaging finding in the context of his significant developmental impairment, although a direct genotype-phenotype relationship cannot be established from conventional karyotyping alone.

The variability of the phenotype is particularly relevant to diagnosis. Individuals with relatively mild manifestations may remain undiagnosed for many years, whereas patients with severe developmental impairment and recognizable dysmorphism may undergo cytogenetic investigation earlier. The increasing availability of chromosomal microarray testing has also expanded recognition of smaller and atypical deletions that may not be readily characterized by conventional karyotyping [1-8].

In the Iraqi context, the present case is noteworthy because it adds 18p deletion syndrome to the group of rare and unusual genetic and dysmorphic disorders that have been clinically documented in Iraqi patients.

The history of medicine demonstrates that important advances do not always begin with large clinical trials, sophisticated molecular laboratories, or population-based studies.

Many discoveries begin with a physician encountering an unusual patient, recognizing a pattern that does not fit established diagnostic categories, documenting the findings carefully, and communicating the observation to the wider medical community.

The documentation of rare, ultra-rare, and previously unrecognized clinical disorders therefore represents an important

component of medical progress.

A single well-documented patient may reveal a previously unrecognized combination of abnormalities, expand the known phenotype of a disease, suggest a new syndrome, identify an unusual association, or provide the first indication that a particular clinical pattern deserves further investigation.

Our clinical work provides an extensive example of this approach. Our published observations, collected in *Encyclopedia of New and Ultra-Rare Disorders: Clinical Discoveries from Iraq and Beyond*, which has been translated into several languages [80-86], describe more than 40 new clinical syndromes and disorders together with more than 30 reports of very rare or ultra-rare disease presentations. The work is characterized by detailed clinical observation, phenotypic documentation, radiological interpretation, longitudinal follow-up, and publication.

A complementary volume, *New Clinical Disorders, Including Genetic and Dysmorphic Syndromes, from Iraq*, focuses specifically on newly documented conditions from Iraq. It identifies 15 unique clinical entities involving neurological, renal, metabolic, endocrinological, developmental, and dysmorphic manifestations [9].

Rare disorders create a particular challenge for medicine because their very rarity limits physicians' opportunities to encounter them. A clinician may see only one patient with a particular phenotype during an entire career. Consequently, unusual presentations can easily be overlooked, attributed to a more familiar disorder, or left unclassified.

The problem becomes more significant when the patient belongs to a population or geographical region that is poorly represented in the international literature.

Our published experience illustrates this problem. For many decades, clinical genetics and dysmorphology had limited representation in the Iraqi medical landscape, with few structured diagnostic pathways, specialized rare-disease centers, or local publications supporting recognition of genetic and dysmorphic disorders. Patients with congenital and inherited conditions could therefore remain undiagnosed or be misclassified.

Documentation can begin to correct this information deficit.

When an unusual disorder is carefully described, the report becomes a permanent source of information that can subsequently be recognized by other clinicians. A second physician encountering a similar patient may recognize the previously reported pattern. Over time, several individual observations may become a recognizable phenotype or syndrome.

Thus, the individual case can become the first building block of collective knowledge.

Our approach involved repeated observation of distinctive phenotypic constellations, exclusion of known disorders, correlation with neuroimaging and laboratory findings, longitudinal observation, and, where possible, replication through additional cases. The resulting observations were subsequently communicated through peer-reviewed publications or academic monographs.

This approach demonstrates that the clinician's task is not limited to assigning an existing diagnostic label. It also includes recognizing when the existing classification is inadequate.

A patient may display:

- an unusual combination of developmental abnormalities;
- a distinctive facial phenotype;
- an unexpected association between two organ systems;
- an unusual radiological finding;
- a familial pattern inconsistent with conventional expectations;
- or a known syndrome accompanied by a previously unreported manifestation.

Such observations may represent variation within a known disorder, an expanded phenotype, a new association, or potentially a new clinical entity. Careful documentation preserves the observation so that subsequent cases can determine its significance.

The importance of clinical documentation becomes particularly apparent in settings where access to advanced genomic investigation is limited.

A clinically recognized syndrome may subsequently become a candidate for genetic investigation. A distinctive phenotype may help researchers determine which patients should undergo sequencing. A familial pattern may provide an initial clue regarding inheritance. A consistent radiological abnormality may become a useful diagnostic marker.

Therefore, clinical documentation and genomic medicine should be regarded as complementary rather than competing approaches.

We have described at least 15 novel clinical conditions documented in Iraq. These included idiopathic hyperuricosuria with hypercalciuria and infantile renal stone disease; syndromic combinations of dysmorphism and neurological abnormalities; ocular and central nervous system abnormalities; hypoparathyroidism with vitiligo, poliosis, and macrocytic anemia; triphalangeal toes with unilateral renal agenesis; distinctive eyebrow and palpebral-fissure abnormalities; schizencephaly with psychomotor retardation and craniofacial abnormalities; unilateral renal hypoplasia; autism associated with precocious puberty; and several other neurodevelopmental and dysmorphic patterns.

The diversity of these conditions is significant. They do not belong to a single specialty. They cross the boundaries of pediatrics, neurology, nephrology, endocrinology, ophthalmology, developmental medicine, and clinical genetics.

This multidisciplinary character is typical of syndromic medicine. A syndrome may only become apparent when findings from different specialties are assembled into one clinical picture.

For example, facial dysmorphism alone may not establish a diagnosis. Similarly, a renal anomaly, developmental delay, or unusual limb configuration may each appear nonspecific when considered separately. When these features occur together in a consistent pattern, however, they may suggest a previously unrecognized syndrome.

Documentation is what allows those relationships to be preserved and communicated.

Phenotyping involves more than recording a diagnosis. It requires detailed characterization of the patient's clinical appearance, developmental history, neurological status, organ involvement, imaging findings, laboratory abnormalities, and, when relevant,

family history.

Imaging provides another important dimension of rare-disease documentation.

Radiological findings can therefore serve several purposes:

1. They may support the recognition of a syndrome.
2. They may distinguish an unusual phenotype from a more common diagnosis.
3. They may reveal previously unrecognized organ involvement.
4. They may provide biomarkers that can be sought in future patients.
5. They may generate hypotheses regarding pathophysiology.

For rare conditions, an unusual imaging sign can become especially valuable because it may help connect apparently unrelated cases.

Rare diseases are not always fully recognizable at the first clinical encounter.

Some manifestations appear later in childhood. Others may change with age or treatment. A finding that is absent during infancy may become obvious several years later.

This is particularly important for developmental and congenital disorders. A child's phenotype can evolve substantially over time. Developmental delay may become clearer as expected milestones fail to appear; dysmorphic characteristics may become more recognizable; neurological manifestations may emerge; and endocrine or renal complications may develop.

When a patient has an unusual combination of abnormalities, there is a natural tendency to fit the patient into the nearest familiar diagnostic category. Such an approach can obscure important differences between the patient's phenotype and the classical description of a known disorder.

A rare-disease clinician therefore needs a degree of intellectual humility: the willingness to acknowledge that the available diagnosis may be incomplete.

The question should not always be:

"Which known disease does this patient have?"

It can also be:

"Does this patient's complete phenotype actually fit the diagnosis?"

That second question can be the beginning of clinical discovery.

Documentation is valuable even when a case does not represent an entirely new disease.

A patient with a known syndrome may exhibit an unusual manifestation that expands the recognized phenotype. Such reports can demonstrate that the boundaries of a disease are broader than previously believed.

Thus, documenting an unusual manifestation can be as scientifically useful as describing a completely new syndrome.

We have previously described first documented Iraqi cases of numerous genetic disorders and syndromes, including Bardet-Biedl

syndrome, genetic vitamin D-resistant hypophosphatemic rickets, Coffin-Siris syndrome, nephropathic cystinosis, Lowe's oculo-cerebro-renal syndrome, Aicardi syndrome, Beckwith-Wiedemann syndrome, Prader-Labhart-Willi syndrome, Lesch-Nyhan syndrome, Hurler-Scheie syndrome, Maroteaux-Lamy syndrome, and others.

We have also described the 35th global case of Cutis Laxa type II, the 130th reported case of Townes-Brocks syndrome, and the 52nd case of Ruprecht Majewski-Bosma syndrome.

These reports are important because they extend the geographical and phenotypic representation of rare disorders.

The ultimate practical value of rare-disease documentation is improved diagnosis.

A published case can become a diagnostic reference for clinicians, and becomes part of a shared diagnostic memory.

The absence of molecular confirmation does not necessarily make a clinical observation scientifically unimportant. A carefully documented case may ultimately become one of the pieces needed to solve a genetic disease.

There is sometimes a tendency to regard individual case reports as less important than large studies. For rare and ultra-rare diseases, however, the case report occupies a special position.

When a disease occurs only in a handful of patients, large randomized or epidemiological studies may not initially be possible. The first evidence must necessarily come from individual observations.

A good rare-disease case report can accomplish several things simultaneously:

- identify a previously unrecognized clinical pattern;
- establish a temporal record of the disorder;
- document an unusual phenotype;
- provide radiological or laboratory evidence;
- alert other clinicians;
- stimulate additional case recognition;
- suggest mechanisms for future research;
- and preserve information that might otherwise disappear with the individual patient.

In this sense, case reporting is not merely descriptive. It is hypothesis-generating medicine.

One of the distinctive features of our work is its geographical origin.

This has scientific importance.

Medical knowledge can become biased toward populations with greater access to specialized centers, genetic testing, and research infrastructure. Documentation from countries and populations that are less represented in biomedical literature helps broaden the clinical picture.

Our published experience therefore illustrates a broader principle:

Clinically important observations can emerge wherever attentive clinicians encounter unusual patients and have the opportunity to

document and publish their findings.

Rare-disease documentation also has an educational function.

Young clinicians need to learn not only the common diagnoses but also how to recognize when a patient does not conform to an established pattern. This is particularly important in pediatrics.

Children with congenital syndromes may initially present with nonspecific findings such as developmental delay, hypotonia, seizures, growth abnormalities, unusual facial characteristics, or organ malformations. The ability to assemble these findings into a coherent phenotype is a clinical skill.

A multidisciplinary approach can convert isolated observations into a coherent syndrome.

For example, a facial phenotype identified by a pediatrician may acquire greater significance when a radiologist identifies a characteristic brain abnormality and a nephrologist identifies a congenital renal anomaly. The combined phenotype may be substantially more informative than any single finding.

Individual reports are essential at the beginning of discovery, but their value increases when cases can subsequently be assembled into registries.

Registries can help answer questions that individual reports cannot:

- How frequently does the condition occur?
- Which manifestations are most consistent?
- Which findings are age-dependent?
- Are there geographical patterns?
- Is the disorder familial?
- Are particular complications more common?
- Do apparently separate syndromes represent the same condition?

Thus, the appropriate trajectory for rare-disease knowledge is not to stop with publication of a case. Rather, the case should serve as an invitation for further observation and collaboration.

The value of documenting rare conditions does not mean that every unusual combination of findings automatically constitutes a new disease.

Most of our 15 newly described conditions were identified through single or limited case observations. They provide important insights, but continued reporting, collaborative research, and integration of genetic tools are necessary for further validation and incorporation into diagnostic classifications.

This distinction is essential.

A single case may generate a hypothesis without proving causation. A distinctive phenotype may represent:

- a genuinely new syndrome;
- an atypical presentation of an existing disorder;
- coincidental coexistence of two conditions;
- an unrecognized environmental factor;

- or a manifestation whose biological significance remains uncertain.

Accordingly, responsible rare-disease documentation requires intellectual humility. The clinician should clearly distinguish observation from interpretation and hypothesis from established fact.

The strongest contribution of a single case may therefore be not that it definitively establishes a new disease, but that it opens a scientifically useful question.

Genomics has transformed the diagnosis of rare diseases. Nevertheless, molecular testing does not eliminate the importance of clinical observation.

Genetic testing requires a clinical question. Phenotyping helps determine which tests are appropriate, how variants should be interpreted, and whether a molecular finding corresponds to the patient's phenotype.

The clinician's eye remains indispensable, particularly in recognizing unexplained presentations and meaningful discoveries remain possible in resource-limited environments through observation, persistence, and publication.

The relationship between clinical medicine and genomics can therefore be viewed as complementary:

The clinician recognizes the pattern;

the laboratory investigates the mechanism;

and subsequent patients determine the reproducibility of the observation.

The significance of our work therefore extends beyond the individual diagnoses. Its broader contribution lies in demonstrating a philosophy of clinical medicine:

Observe carefully.

Question unusual patterns.

Document completely.

Follow patients over time.

Compare observations with existing knowledge.

Publish unusual findings.

Encourage others to replicate them.

This philosophy preserves the traditional strengths of bedside medicine while connecting them to modern genetic and biomedical research.

To our knowledge, the case described here appears to be the first documented Iraqi case of Jean De Grouchy syndrome (18p deletion syndrome) reported in the medical literature.

An additional strength of the present report is the combination of a characteristic clinical phenotype, conventional cytogenetic confirmation of 18p deletion, and brain CT findings.

Conclusion

This book documents a clinically recognizable case of Jean de Grouchy syndrome (18p deletion syndrome) in Iraq. The combination of significant developmental and intellectual impairment, characteristic dysmorphic features, conventional cytogenetic

confirmation of 46, XY, 18p–, and associated mild cerebral volume loss supported the diagnosis.

To our knowledge, this appears to be the first documented Iraqi case of Jean de Grouchy syndrome reported in the medical literature.

The case highlights the value of careful clinical phenotyping, cytogenetic investigation, and neuroimaging in the recognition and documentation of rare chromosomal disorders.

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All the necessary consents have been obtained.

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