Musculoskeletal Medicine and Pain

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Structural abnormalities and osteopathic considerations in primary immunodeficiencies

https://doi.org/10.1515/jom-2022-0129
Received July 5, 2022; accepted January 4, 2023; published online January 25, 2023

Abstract: Structural skeletal abnormalities are associated with primary immunodeficient (PID) patients. These abnormalities have not been well studied in PID with reference to osteopathic medicine tenets. Osteopathic structural examinations of PID patients with respect to these tenets and the diagnosis of somatic dysfunctions preventing the free flow of lymph fluids back into the circulation and the disruption of the skeletal microenvironment may have an impact on the status of the immune system in patients with a PID. A standardized evaluation was conducted in a patient with a phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) mutation who presented with skeletal abnormalities. A literature review was also conducted to determine the breadth of other PIDs with structural irregularities. Osteopathic structural clinical examinations (OSCEs) were performed by an osteopathic medical student, fellow, and attending after receiving informed consent from the patient. The findings were collected regionally noting severity, tissue texture changes, asymmetry, altered range of motion (ROM), and tenderness according to DO-Touch.NET physical examination and treatment form. A literature review was conducted utilizing various search engines and the textbook, Stiehm’s Immune Deficiencies, 4th edition. The significant findings found from the patient were right sidebending rotation cranial strain pattern with decreased left temporal bone motion, temporomandibular joint crepitus, and right deviation upon mandibular opening. The thoracolumbar region revealed tissue tenderness and restricted psoas ROM. Bilateral sacroiliac joint tenderness, right superior sheering, and anterior innominate rotation, along with left-on-left sacral flexion, were associated with valgus knees. The literature search showed multiple other PIDs outside of PIK3R1 that have associated skeletal and structural abnormalities. Irregular skeletal features found in immunodeficient patients may have an additive defect on the immunological responses due to somatic dysfunction impinging on the lymphatic flow to the central circulation. Other different immunodeficient patients suffer from bone structural abnormalities, which may lead to further immune hindrance caused by impingement of flow as well as bone marrow microenvironment impact on the peripheral immunological output. We present the first osteopathic examination with detailed findings of somatic dysfunction in a patient with PID. Future studies on PID patients should require more attention to structure and function, as found by a thorough osteopathic examination in order to unrestrict preformed cellular and humoral components back into the peripheral circulation.

Keywords: neuromusculoskeletal; osteopathic structural clinical exam; PIK3R1; primary immunodeficiency.

The interrelation of structure and function is an important tenet of osteopathy that applies to the central and peripheral immune system [1]. These interrelationships may convey a functional relevance to the immune system due to its effect on movement of lymph and its effects on the microenvironments of bone marrow [2].

The boney structural abnormalities in patients with immune deficiencies may be an additive effect on their immunological responses. Gharib and Gupta [3] have previously described 96 primary immunodeficiencies associated with these abnormalities. A comprehensive evaluation of structural boney lesions in primary immunodeficiencies...
(PIDs) in reference to an osteopathic examination has not been done previously. We have described the first concise osteopathic examination of an immunodeficient patient with a phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) mutation and a review of musculoskeletal abnormalities found in more common PID.

Case report

We present a 28-year-old White female with a PID associated with B cell abnormalities and PIK3R1 heterozygous gene mutation (c.1425 + 1G>A). She presented to the clinic in June 2019. Her anterior craniofacial structural anomalies had been previously described [4] and became more pronounced with age: triangular facies, ocular depression, lipodystrophy, and hypoplastic nasal alae (Figure 1). Informed consent was obtained on paper by author Marija Rowane, and an osteopathic structural clinical examinations (OSCEs) was independently performed by an attending, fellow, and osteopathic medical student, without disclosing findings until concluding each regional evaluation [5]. The use of three evaluators was utilized in order to mitigate any errors in the evaluation of the patient’s osteopathic examination. Severity, tissue texture changes, asymmetry, altered range of motion (ROM), and tenderness were organized under anatomical regions in the DO-Touch.NET Physical Examination and Treatment Form (Table 1) [5, 6]. Discrepancies were re-evaluated to confirm the diagnoses, and the table displays the consensus of the evaluators.

An extensive literature search was performed by author MC and reviewed by mentor RH utilizing the standard immunological text from Stiehm’s Immune Deficiencies textbook published in 2022 (Editors: Kathleen E. Sullivan and E. Richard Stiehm) by reviewing for musculoskeletal issues. An additional literature review was conducted utilizing PubMed, Google Scholar, OSTMED.DR, AOA Osteopathic Research Database, American Academy of Osteopathy Journal – Index, Osteopathic Research Web, CORE, iSEEK, BASE, and MEDLINE. The search terms that were utilized

Figure 1: Craniofacial presentations of a 28-year-old female patient with phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) mutation. (A) Anterior view. (B) Lateral view.
Table 1: Osteopathic structural clinical examination (OSCE) consensus findings of somatic dysfunction in phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) mutation primary immunodeficiency.

<table>
<thead>
<tr>
<th>Region</th>
<th>Side (R/L)/vertebra(e)</th>
<th>Severity</th>
<th>TART</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 1 2</td>
<td>Tt As</td>
<td>R sidebending rotation (↑ extension, ↓ flexion; L temporal bone motion “locked”, ↑ motion on R)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRI 12 cycles/min</td>
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<td></td>
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<td></td>
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<td>TMJ bilateral crepitus (R&gt;L), R mandibular deviation</td>
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<tr>
<td>Cranium/face</td>
<td>X</td>
<td>X X X</td>
<td></td>
<td>Cranial strain pattern: R sidebending rotation</td>
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<td></td>
<td></td>
<td></td>
<td>As</td>
<td>C1 RsSs, C2 NRsSs, C3 RsSs (--) spurling maneuver</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rr</td>
<td>T3 FrsS rotational ease</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Te</td>
<td>Prominent L paravertebral musculature</td>
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<td></td>
<td></td>
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<td></td>
<td>Mild kyphosis</td>
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<td>T7 transition of prominent paravertebral musculature from L (upper thoracic region) to R</td>
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<tr>
<td>Thorax</td>
<td>T1–4</td>
<td>X X X X X</td>
<td></td>
<td>T12 L hypertonicity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Expiratory ribs (inspiratory restriction)a</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CTJ T1 RsSs</td>
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<td>Inspiratory ribs (inspiratory restriction)</td>
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<td></td>
<td></td>
<td>CTJ L rib 1 S (mid-clavicular)</td>
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<td></td>
<td>Bilateral sacroiliac joint tenderness</td>
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<td></td>
<td>L-on-L sacral torsion [(↑) R SFTSE; R PSIS S/F, R A/D sacral sulcus, L P/S inferior lateral angle]</td>
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<td></td>
<td></td>
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<td>Superior and posterior innominate rotation (PSIS I/ASIS S)</td>
</tr>
<tr>
<td>Pelvis/innominate</td>
<td>R</td>
<td>X X X X X</td>
<td></td>
<td>Arm length shorter (styloid process) with superior shear, R clavicular ease with I motion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm length longer (styloid process) with inferior shear, L clavicular ease with S motion</td>
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<td></td>
<td>(--) Radiculopathy/Lasegue’s test; (--) Patrick FABER; SLT (65°); long restrictors R (psoas-piriformis); dorsiflexion elicits pain</td>
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<td>(--) Radiculopathy/Lasegue test; (--) Patrick FABRE; SLT (75°); long restrictor (psoas) mild-moderate Rr</td>
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<tr>
<td>Distal lower</td>
<td>R</td>
<td>X X X X X</td>
<td></td>
<td>Leg length shorter (M malleolus); dorsiflexion elicits less pain</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pes planus (M longitudinal arc Rr, pronounced supination)</td>
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<td></td>
<td></td>
<td></td>
<td>Leg length longer (M malleolus)</td>
</tr>
<tr>
<td>Knee/calf/shin</td>
<td>R</td>
<td>X X X X X</td>
<td></td>
<td>Valgus knees, R</td>
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<td>Valgus knees, R L&gt;R (25°)</td>
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<td></td>
<td>Short stature</td>
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<td>Hypotonia (exaggerated when sedentary)</td>
</tr>
</tbody>
</table>

Adapted categorization from Degenhardt et al.’s DO-Touch.NET Physical Examination and Treatment Form. *The patient expressed mild tenderness to palpation (TTP) in these areas. R, right; L, left; TART, Tt, tissue texture changes; As, asymmetry; Rr, restricted range of motion; Te, tenderness; ↑, increased; ↓, decreased; CRI, cranial rhythmic impulse; TMJ, temporomandibular joint; C, cervical; R, rotated; S, sidebent; N, neutral; (→), negative; T, Thoracic vertebral levels; F, flexed; CTJ, cervicothoracic junction; S, superior; P, posterior; (+), positive; ASIS, anterior superior iliac spine; SFTse, Seated Flexion Test; PSIS, posterior superior iliac spine; A, anterior; D, deep; SFTst, Standing Flexion Test; L, inferior; FABER, Flexion, Abduction, External Rotation; SLT, Straight Leg Test.
included “osteoathy”, “musculoskeletal”, “immune”, “skele
tal dysplasia”, “skeletal”, and “PID”, and by searching the
specific PIDs found within the previously mentioned Stiehm’s Immune Deficiencies textbook.

The most significant findings of the osteopathic exami
nation included a right sidebending rotation cranial strain pattern with decreased left temporal bone motion, tempo
rromandibular joint crepitus, and right deviation upon
mandibular opening. The thoracolumbar region revealed
tissue tenderness and restricted psoas ROM. Bilateral sacroiliac joint tenderness, right superior sheering, anterior
innominate rotation, and left-on-left sacral flexion were
associated with valgus knees.

**Discussion**

The skeletal frame to which the muscles, nerves, vessels, and
connective tissue suspend serves as the fulcrum for the
movement of the structure and bodily fluids. Movement allows for the fluids of the lymph system containing pre
determined immunoglobulins and T cells to flow to an
inflammatory or homeostatic site of the body for repair,
infection fighting, or maintenance [7]. Although this may suggest that the bone is only an observer in the process, it
also provides a microenvironment within which the
immune precursors may develop and prepare for departure
into the nonosseus structure. This science has been charac
terized as osteoimmunology [2].

Although the understanding of osteoimmunology may reflect the immune system's effect on bone disorders, it also
focuses on the effects of the bone structure on immune
development. Aberrations of the structure of the bone may
impact the output of effector cells of both innate and adaptive
immune systems such as what are found in many pri
mary immunodeficiencies such as DiGeorge syndrome [8],
ADA deficiency [9, 10], signal transducer and activator of
transcription 3 (STAT3) and 5b mutations [11, 12], cartilage
hair hypoplasia [13], and PIK3R1 mutations (described pre
viously). Although the aberrancies of the skeletal structure
do not play a role in the isolated molecular mutations found
in such immune issues, these aberrancies may contribute to
the overall immunological responses. A review of the
structural abnormalities have not been performed in the
literature, possibly due to the rarity of these disorders.

A mutation in PIK3R1 causes broad immune def
iciencies, such as low serum immunoglobulin G (IgG) and A
(IgA) levels with elevated IgM that progressed to an absence
of IgM over the course of intravenous immunoglobulin
replacement therapy [4]. The characteristic skeletal
abnormalities associated with this syndrome include short
stature, triangular facies, hypoplastic nasal alae, and other
anterior facial bone abnormalities [9].

Combined immune deficiencies have been associated
with structural abnormalities. Adenosine deaminase severe
combined immunodeficiency (ADA-SCID) is a genetic defect
causes immune deficiency due to the accumulation of pu
rines within the lymphocytes [14]. The aggregation of these
molecules can manifest as lymphopenia and recurrent in
fections. This multiorgan disorder commonly presents with
skeletal abnormalities and defects. These are due to
improper osteoblast activity leading to reduced bone volume
and formation [14]. This has manifested previously as flared
ribs, leading to a rachitic rosary [15], large low-set ears, and
small bones [8].

Isolated T cell defects have been associated with struc
tural abnormalities. DiGeorge syndrome is a genetic disor
der caused by a 22q11.2 microdeletion [16]. One of the
hallmarks of this disease is a hypoplastic or absent thymus,
which leads to immune deficiencies caused by abnormal
T cell development [16, 17]. The characteristic skeletal defects
of these patients involve the cranium, jaw, palate, and other
facial defects [18]. These structural irregularities can be the
root of somatic dysfunctions, and osteopathic considera
tion should be given to these patients to enhance their bodily
function.

B cell defects caused by STAT3 mutations in Hyper-IgE
have also been associated with skeletal issues. Hyper-IgE
syndrome can be caused by numerous mutations, but the
autosomal dominant STAT3 mutation is the most prevalent
[19]. The normal triad of symptoms is eczema rashes, cold
skin abscesses, and recurrent sinopulmonary infections [19].
There are many nonimmunologic clinical features of this
disease including characteristic facies, hyperextensibility,
and scoliosis [19].

Generalized bone growth defects has been associated
with immunological aberrancies. Cartilage-hair hypoplasia
(CHH) is a rare disorder caused by a mutation in the RNA
component of the mitochondrial RNA processing endonu
lease (RMRP) RNA gene causing immune deficiencies in
both cellular and humoral immunity [20]. In addition to
immune dysregulation, CHH presents with growth defects,
scoliosis, lumbar lordosis, thin hair, and cranial growth
abnormalities [21].

Other immunodeficiencies associated with skeletal
abnormalities are described elsewhere, but individual dis
cussion is beyond the scope of this article [3]. Skeletal fea
tures found in immunodeficient patients, such as the one
describe with PIK3R1 mutation, suggest that there may be
additive effects on PID immunological responses.
Conclusions

Although manipulation of the skeleton has been shown not to influence the immune system, its ability to act as a fulcrum or motion, to allow flow of effector cells through lymph and its internal microenvironment, for immune development points to the importance of a full osteopathic structural examination in patients with PIDs [22]. We have described the first concise osteopathic examination of an immunodeficient patient with a PIK3R1 mutation and a review of musculoskeletal abnormalities found in more common PIDs. Our study and review of the literature does not completely identify all of the PIDs that have an associated skeletal disease due to the lack of attention to the skeletal system in these disorders.

Acknowledgments: The authors thank Brain Degenhardt, DO (Director of DO-Touch.NET and A.T. Still Research Institute of A.T. Still University) for his protocol recommendations on evaluating the patient with the DO-Touch.NET Physical Examination and Treatment Form.

Research funding: None reported.

Author contribution: All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; M.A.C. drafted the article or revised it critically for important intellectual content; R.W.H. authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None reported.

Informed consent: Written and verbal informed consent was obtained from the patient for the Osteopathic Structural Clinical Examination and educational presentation of deidentified patient information and images.

References


