Electrolyte Imbalance in Anti-LGI1 Encephalitis
It Is Not All in Your Head

Avi Gadoth, MD, Michal Nisnboym Ziv, MD, Yifat Alcalay, PhD, Asia Zubkov, MD, Idit Schwartz, MD, Doron Schwartz, MD, Marana Abboud, MSc, Tamar Rubinek, PhD, Ofer Yossepowitch, MD, and Talia Weinstein, MD, PhD

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Abstract

Background and Objectives
Antileucine-rich glioma-inactivated 1 (anti-LGI1) autoimmune encephalitis was first described in 2010 and is today the most common type of limbic encephalitis. During the course of the disease, 60%–88% of the patients develop hyponatremia. The etiology of the sodium disorder is unclear, often presumed to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Other electrolyte abnormalities have not been reported in association with anti-LGI1 antibody encephalitis. Due to the presence of hypomagnesemia and hypophosphatemia in our patients, we set out to try to find the expression of LGI1 protein in the kidney as an explanation for these abnormalities.

Methods
We reviewed the medical files of all patients diagnosed with anti-LGI1 antibody encephalitis, at the Department of Neurology in the Tel Aviv Medical Center between January 2011 and December 2020, exploring for electrolyte abnormalities. Using tissue staining, Western blot, mass spectrometry, and RNA expression techniques, we tried to demonstrate the expression of LGI1 protein in the human kidney.

Results
We identified 15 patients diagnosed with anti-LGI1 antibody encephalitis. Their average age was 65 years (44–80), and 9 were male individuals. Thirteen of the 15 patients (87%) developed varying degrees of hyponatremia. Laboratory studies demonstrated low serum osmolality, low serum blood urea nitrogen, and low uric acid, with a high urinary sodium and inappropriately high urine osmolality, supporting the presumable diagnosis of SIADH. One patient with hyponatremia that was tested, had high levels of copeptin, supporting the diagnosis of SIADH. In addition to hyponatremia, 7 patients (47%) exhibited other electrolyte abnormalities; 5 patients (33%) had overt hypophosphatemia, 4 patients (27%) had overt hypomagnesemia, and 2 other patients (13%) had borderline low magnesium levels. Western blot analysis of human kidney lysate, mass spectrometry, and qRT-PCR failed to demonstrate the expression of LGI1 protein in the kidney.

Discussion
Hyponatremia in patients with anti-LGI1 antibody encephalitis is due to SIADH as previously assumed. Other electrolyte abnormalities such as hypomagnesemia and hypophosphatemia occur in at least 40% of patients and may be another clue for the diagnosis of anti-LGI1 antibody encephalitis. Because we failed to demonstrate LGI1 expression in the kidney, the results of our study suggest that renal losses lead to these disturbances, most probably due to SIADH.

From the Department of Neurology (A.G.), Encephalitis Center, Tel-Aviv Medical Center; Department of Neurology (M.N.Z.), Sourasky Tel Aviv Medical Center, Sackler School of Medicine, Tel Aviv University; Encephalitis Center (Y.A.), Immunology Laboratory, Sourasky Tel Aviv Medical Center; Department of Pathology (A.Z.), Tel Aviv Medical Center; Department of Nephrology (I.S., D.S., T.W.); Oncology Division (M.A., T.R.); and Department of Urology (O.Y.), Sourasky, Tel-Aviv Medical Center, Sackler School of Medicine, Tel Aviv University, Israel.

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

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**Introduction**

Antileucine-rich glioma-inactivated-1 (LGI1) autoimmune encephalitis was first described in 2010\(^1\)\(^2\) and is today the most common antibody found in limbic encephalitis.\(^3\) The clinical presentation of this illness includes subacute cognitive decline, short-term memory loss, behavioral changes, and seizures.\(^4\) The wide field of symptoms and syndromes pose a diagnostic challenge due to the broad differential diagnosis, focal seizures initially not recognized to be seizures, and normal ancillary testing in the beginning in many cases.

During the course of the disease, 60%–88% of the patients develop hyponatremia, mainly mild to moderate, but which also may be severe and life-threatening.\(^1\)\(^4\)\(^6\) On presentation, the occurrence of seizures is often attributed to hyponatremia, thus delaying the diagnosis of underlying encephalitis. It is possible that hyponatremia may precede the neurologic symptoms in anti-LGI1 encephalitis, but because patients are usually not tested for electrolytes until the neurologic manifestations, there is no significant evidence for that. The etiology of the sodium disorder is unclear, often presumed to be the result of the syndrome of inappropriate diuretic hormone secretion (SIADH).\(^7\) Rapid diagnosis and initiation of the appropriate treatment is the most pertinent step in patient management.

Recently, we treated a patient who presented with severe hyponatremia, attributed to anti-LGI1 antibody encephalitis. The clinical presentation prompted us to review the records of all patients diagnosed with this disease at the Tel Aviv Medical Center, between January 2011 and December 2020.

We hereby describe 15 patients with anti-LGI1 antibody encephalitis, of whom 13 exhibited hyponatremia during the course of their disease. In addition to hyponatremia, several patients demonstrated other electrolyte disorders including hypophosphatemia and hypomagnesemia, which have not been previously described in association with this syndrome.

These unexpected findings in patients with anti-LGI1 encephalitis encouraged us to explore the possibility that perhaps LGI1 is expressed also in the kidney, contributing to the abnormalities in electrolyte balance. We therefore performed studies on human kidney by using immunohistochemistry, Western blotting, RNA expression, and mass spectrometry.

**Methods**

**Standard Protocol Approvals, Registrations, and Patient Consents**

The study was approved by the IRB of the Tel Aviv Medical Center.

**Glossary**

ADH = antidiuretic hormone; LGI1 = leucine-rich glioma-inactivated 1; MoCA = Montreal Cognitive Assessment; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

**Patients**

A review of the medical files of all patients diagnosed with anti-LGI1 antibody encephalitis at the Department of Neurology in the Tel Aviv Medical Center between January 2011 and December 2020 identified 15 patients of whom 13 manifested hyponatremia <135 mEq/L during the course of their disease. Clinical data retrieved from the files included symptom presentation, blood pressure, laboratory tests, treatment regimens, and outcomes.

**Antibody Testing**

Autoimmune encephalitis panel (Euroimmun, Lübeck, Germany) using a cell-based assay with indirect immunofluorescence that includes anti-NMDA, anti-GABA-B, anti-AMPA, anti-LGI1, and anti-CASPR2 was used to detect LGI1 positivity. Samples of all 15 patients were tested in the serum; 7 were additionally tested on the CSF.

**Tissue Staining**

Immunohistochemistry was performed on 5-mm paraffin-embedded sections of normal kidney tissue, using a 3-step indirect process based on the label-strep avidin-biotin peroxidase complex method. Immunohistochemistry was performed using the DAB I VIEW detection kit (ROSH-VENTANA) that uses biotinylated secondary antibodies to locate the bound primary antibody, followed by the binding of streptavidin-horseradish peroxidase conjugate.

The complex was then visualized with hydrogen peroxidase substrate and 3,3-diaminobenzidine DAB tetrahydrochloride chromogen, which produces a dark brown precipitate that is readily detected by light microscopy.

Antibodies used were anti-LGI1–specific IgG (Polyclonal, ab30868, Abcam, Cambridge, UK) and biotinylated Ig secondary antibody (Ventatana, AZ).

**Western Blot**

Human kidney lysate was obtained from a healthy section of a kidney removed from a patient with renal cell carcinoma. The lysate was prepared by homogenization in RIPA buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% NP-40, 0.25% Na-deoxycholate, 1 mM EDTA, 1 mM NaF) together with a protease inhibitor cocktail (Sigma, St. Louis, MO). Tissue and cell debris were removed by centrifugation at 12,000 rpm for 20 minutes. Protein concentration was determined using Pierce BCA Protein Assay kit (Thermo Fisher Scientific, Waltham, MA). Lysates were resolved on 10% SDS-PAGE and immunoblotted with the indicated antibodies. Human brain lysate (NB820-59177) was purchased from Novus Biologicals (Centennial CO) and served as a positive control.
Antibodies
LGI1 rabbit polyclonal antibody (12483-1-AP) was purchased from Proteintech© (Rosemont, IL). LGI1/EPT (ab228613) antibody was purchased from Abcam (Cambridge, UK).

RNA Expression
Human kidney and brain total RNA were purchased from Takara (Takara Bio Inc., Shiga, Japan). Total RNA (1 μg) was reverse transcribed using qScript cDNA synthesis kit (Quanta bio, Beverly, MA). Real-time PCR assay was performed with TaqMan Gene Expression Assay (Applied Biosystems) with specific probe in triplicates using StepOne Plus (Applied Biosystems). All TaqMan probes were labeled at the 5'-end with the fluorescent dye 6-carboxyfluorescein (FAM) as reporter and at the 3'-end with 6-tetramethylrhodamine (TAMRA) as fluorescent quencher. Specific primers for LGI1 (Hs0018508 PN4448892) and Klotho (Hs00934627) were used. Equal loading was determined using HPRT1-specific primers (Hs 99999909 PN4453320).

Mass Spectrometry
Mass spectrometry analysis was conducted by Smoler Protein Research Center, Technion. Eluted proteins were run in SDS-PAGE 10%, stained with Imperial protein stain (Thermo Scientific, Pittsburgh, PA), according to the manufacturer’s instructions. Then, lanes were excised and subjected to mass spectrometry analysis. To this aim, samples were digested by trypsin and analyzed by LC-MS/MS on Q Exactive plus (Thermo Scientific). Data were analyzed with Discoverer 2.4 identification software with the search algorithm: Sequest (Thermo Scientific) search engine. Data were filtered with 1% false discovery rate in the peptide level and in the protein level.

Data Availability
Data will be available in full on request.

Results
Case Report
A 76-year-old woman was admitted to the Neurology department in July 2018 due to a generalized tonic-clonic seizure. The patient and her family denied any seizures in the past, yet mentioned a slowly progressive cognitive decline that began 2 years previously. Eight months before her admission, she was examined by a neurologist who described a Montreal Cognitive Assessment (MoCA) battery score of 24/30 with mainly short-term memory difficulties. In the week before her admission, she described short episodes of presyncope and general weakness. Her medications included 50 mcg of eltroxin, 10 mg of rosuvastatin, and 20 mg of pantoprazole.

On admission, she was in a postictal state. Serum sodium was 128 mEq/L (normal range 135–146 mEq/L), serum osmolality was 275 mosmol/kg (normal range 285–295 mosmol/kg), and the remainder of her blood chemistry and complete blood count tests were within normal limits. A brain CT scan was unremarkable. Lumbar puncture was unrevealing with no WBC, and protein and glucose levels were within the normal ranges (35 mg/dL, 68 mg/dL respectively).

The following day the patient returned to her baseline cognitive condition as described by her family. Laboratory results showed low serum sodium of 132 mEq/L, potassium of 3 mEq/L (normal range 3.5–5.3), chloride of 93 mEq/L (normal range 95–110), and phosphorus of 1.62 mg/dL (normal range 2.5–4.5). Magnesium, 2.15 mg/dL (normal range 1.8–2.55), and TSH, 0.73 mU/L (normal range 0.4–4.7), were within normal ranges. EEG demonstrated left and right independent temporal epileptiform activities, and the MoCA score was 16/30. After fluid restriction, serum electrolytes normalized. However, on the seventh day of admission, the patient became sleepy and hardly communicated; laboratory studies showed a hyponatremia of 116 mEq/L. Potassium, calcium, and phosphorus levels were within normal limits. Urine sodium was 200 mEq/L, and urine osmolality was 439 mosmol/kg, suggesting the diagnosis of SIADH. Cell-based assay was positive for LGI1, both in her serum and in her CSF, and a diagnosis of anti LGI1 antibody encephalitis was established. Treatment with hypertonic 3% NaCl and IV methylprednisolone led to a gradual increase in serum sodium levels until they normalized within 10 days.

Case Series
Table 1 summarizes the clinical and laboratory measures in the cohort. Figure 1 presents the hyponatremia timeline in comparison with the major neurologic clinical symptoms and response to treatment. Fifteen patients were included in the study; all tested positive in the serum for LGI1 and 2 of 7 tested in the CSF were positive. The average age of patients was 65 years (44–80), and 9 were male individuals. Thirteen patients developed varying degrees of hyponatremia during the course of their disease. Hyponatremia was severe in 5 patients (<120 mEq/L), requiring treatment with hypertonic 3% NaCl, moderate (120–129 mEq/L) in 3 patients, and mild (130–134 mEq/L) in 5 patients. Among the 13 patients who had hyponatremia, symptom onset before admission was between 3 days and 12 months; in most of the patients, sodium levels were not tested before admission, and therefore, onset of hyponatremia was set as the admission date. Immunomodulatory treatment was initiated in 10 patients between 0 and 45 days after admission while 2 patients developed hyponatremia while on treatment and 1 patient did not receive treatment in our center. On physical examination, all patients were euvolemic, with normal blood pressure, and no apparent hypovolemic stimulus. Laboratory studies demonstrated low serum osmolality, low serum blood urea nitrogen, and low uric acid, with a high urinary sodium and inappropriately high urine osmolality, thus supporting the presumable diagnosis of SIADH.

To identify possible other causes of hyponatremia, we explored the patients’ clinical records and found that only 3 patients were previously treated with diuretics, and all patients had TSH levels within normal limits. None of the patients received vasopressin inhibitors or demeclocycline. In addition, none of the
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<th>Serum magnesium (mg/dL)</th>
<th>Serum osmolality mosmol/kg</th>
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All abnormal values are bold.
^a Low value.
^b Borderline.
patients received IVIG before hyponatremia onset, which may cause pseudohyponatremia; thus, there was no evidence of another disorder leading to hyponatremia.

In addition to hyponatremia, 7 patients (47%) exhibited other electrolyte abnormalities; 5 patients (33%) had overt hypophosphatemia: median 1.79 mg/dL (range 1.09–2.4, normal range 2.5–4.5); 4 patients (27%) had overt hypomagnesemia: median 1.64 mg/dL (range 1.41–1.67, normal range 1.8–2.55); and 2 other patients (13%) had borderline low magnesium levels (1.81, 1.89 mg/dL).

Hypomagnesemia and/or hypophosphatemia in those patients persisted at least a week after a generalized seizure (in 5 patients who had a generalized seizure) and was present in 2 patients who did not have generalized seizures.

In the most recently diagnosed patient (number 15 in Table 1), we performed additional studies to identify a possible etiology for her hypomagnesemia and hypophosphatemia. Twenty-four–hour urine collections revealed a fractional excretion of magnesium of 4.48% and a fractional excretion of phosphate of 12.71%, implying renal loss of these electrolytes. Her plasma level of copeptin proAVP in a nonwater-deprived state revealed an elevated value of 20.7 pmol/L (normal <13.1; performed at Mayo Clinic Laboratories). Table 2 describes the treatment and outcomes of the cohort.

**Localization of LGI1**

Immunohistochemistry studies in normal human kidney demonstrated diffuse LGI1 staining; however, blood vessels were also stained, suggesting that this was not specific (Figure 2). Western blot analysis of human kidney lysate compared with that of brain lysate identified LGI1 expression only in the brain (eFigure 1, links.lww.com/NXI/A885).

To further explore the expression of LGI1 in the kidney, qRT-PCR was performed with a specific probe for LGI1 gene. Commercially purchased human kidney and brain total RNA extracts served as templates for the qRT-PCR. The results showed that LGI1 was not expressed in the kidney when compared with that in the brain tissue, Mass spectrometry results also indicated LGI1 presence only in the brain.

Klotho is a protein abundantly expressed in the kidneys and was used as a positive control (PMID: 9363890). Indeed, both Western blot and qRT-PCR analysis demonstrated a high klotho expression in the kidney. Thus, using different methodologies, we failed to demonstrate LGI1 presence in the kidney.

**Discussion**

In this study, we describe that patients diagnosed with anti-LGI1 antibody encephalitis at our center had a high incidence of hyponatremia during the course of their disease. Hyponatremia is a characteristic feature of anti-LGI1 antibody encephalitis with a reported occurrence of 60%–88%. It is usually mild to moderate but may also be severe. Hyponatremic encephalopathy is a serious complication of hyponatremia and can result in permanent neurologic impairment or death. Frequently, in patients undergoing evaluation for seizures, and before the diagnosis of anti-LGI1 antibody encephalitis, seizures and neurologic manifestations might mistakenly be attributed to hyponatremia. A delay in establishing the correct diagnosis may lead to refractory hyponatremia, which is not responsive to treatment until limbic encephalitis is recognized and treated appropriately.

Although documented for a decade, the explanation for the association of hyponatremia with anti-LGI1 antibody encephalitis...
is still unclear. As demonstrated in this study, many patients present with clinical and biochemical features of SIADH.

In healthy individuals, water intake determines urine output by altering plasma osmolality. Antidiuretic hormone (ADH), which is produced in the hypothalamus, and released from the posterior pituitary, controls renal water handling. Osmoreceptors in the hypothalamus regulate ADH secretion in response to plasma osmolality, which in turn modifies collecting tubule permeability to water. In the absence of ADH, the urinary osmolality can fall to 50 mOsm/kg H₂O, leading to high water excretion. Therefore, hyponatremia occurs only when there is a defect in renal water excretion, such as in the circumstance of fixed ADH release. The hallmarks of SIADH are mild volume expansion with

Figure 2 Kidney Immunohistochemistry

![Kidney Immunohistochemistry](image)

(A and B) Show diffuse staining in kidney for LGI1. Arrows point at kidney blood vessels strongly stained representing nonspecific staining.
low-to-normal plasma concentrations of creatinine, urea, uric acid, impaired free water excretion with relatively high sodium excretion, and hyponatremia that is relatively unresponsive to sodium administration in the absence of fluid restriction.

Determination of ADH levels is difficult due to their very short half-life. Copeptin is a glycoprotein that contains the C-terminus of preprovasopressin. It is stable and correlates well with ADH levels and is used as a surrogate marker of ADH in the assessment of water balance disorders. In this study, patient 15 who developed hyponatremia of 129 mEq/L and was in a non-water-deprived state demonstrated elevated plasma copeptin proAVP, supporting the diagnosis of SIADH.

Studies in animal models have shown that LG1 is highly expressed in the hypothalamus. This finding supported the notion that an inflammatory response targeting LG1 in the hypothalamus and disrupting normal regulatory function of ADH secretion is the cause of hyponatremia. A study on transgenic mice demonstrated LG1 expression in kidney tubules. This raised the possibility of a direct antibody effect on these tubules, leading to hyponatremia.

In addition to hyponatremia that is compatible with the diagnosis of SIADH, we report that in our cohort, 40% of patients exhibited low serum levels of magnesium, phosphate, or both and an additional 3 patients exhibited borderline magnesium values. Several patients required electrolyte supplementation. A recent case study in New England Journal of Medicine described a patient with anti-LGI1 antibody encephalitis who manifested hypomagnesemia in addition to hyponatremia. However, a possible explanation for the hypomagnesemia was not discussed.

Under normal conditions, 70% of the filtered magnesium is reabsorbed in the thick ascending loop of Henle and 10% in the distal convoluted tubule. The latter determines the final urinary magnesium excretion. In hypomagnesemia, the kidney increases the reabsorption, and consequently, the fractional excretion is lower than 1%. Reabsorption of magnesium is closely coupled with the reabsorption of sodium in the distal tubule. Genetic disorders that reduce sodium reabsorption in the distal tubule are associated with hypomagnesemia. In SIADH, there is expansion of the extracellular fluid volume, which triggers increased urinary sodium excretion and thereby may lead to decreased passive magnesium reabsorption. In our study, the patient with established SIADH demonstrated a fractional excretion of magnesium of 4.48%, indicating increased renal magnesium losses.

Regarding phosphate reabsorption, approximately 60%–70% occurs in the proximal tubule and 10%–15% in the distal tubule. In patients with hypophosphatemia, fractional excretion above 5% is indicative of renal phosphate wasting, which in our patient was 12.71%. It has been previously shown that ADH infusion leads to markedly increased fractional phosphate excretion. These combined results indicate that our patient with confirmed SIADH developed hypophosphatemia and hypomagnesemia due to inappropriate renal losses.

Hypophosphatemia and hypomagnesemia are not classical features of SIADH. We suggest, based on our findings, that as a consequence of the development of SIADH and increased loss of sodium in the urine, there are secondary physiologic changes in tubular reabsorption, which lead to hypomagnesemia and hypophosphatemia. If the serum levels of these electrolytes are significantly low, replacement therapy should be initiated to restore normal values. However, on recovery from encephalitis and resolution of SIADH, these disturbances resolve spontaneously, as observed in our cohort.

In a study aimed to derive LG1 tissue-specific expression, transgenic mice carrying LG1 were generated. Apart from distinct regions of the brain, LG1 was demonstrated in individual tubules and sympathetic ganglia in the kidney. In this study, kidney tissue demonstrated LG1 staining; however, blood vessels were also stained (Figure 2), suggesting that this was not specific.

Due to the discrepancy with previous reports, we meticulously assessed LG1 expression using mass spectrometry analysis and Western blot to identify the protein and qRT-PCR to reveal mRNA expression. Using these methods, we were not able to detect LG1 protein in the kidney, whereas it was abundant in the brain, which served as a positive control. This was also evident using qRT-PCR. Moreover, analysis of public databases (Protein Atlas or maayanlab.cloud/Harmonizome/gene/LGI1) further substantiated our results that LG1 is not expressed in the kidney. Furthermore, the Harmonize database showed that while LG1 was highly expressed in prostate cell lines such as ALVA 31, its expression was among the lowest in renal cells such as ACHN.

Regarding LG1 expression in murine kidney—while it was shown that LG1 is expressed in specific cells in mouse kidney, LG1 was not observed in human kidney, not by us, neither in public databases or in the literature. Furthermore, analysis of gene expression (SAGE) libraries, generated from the glomerulus and 7 anatomically defined nephron segments from mouse and human kidneys, for serial expression, identified 4,644 pairs of gene orthologs expressed in 1 or both species. Poor conservation of gene expression was found, with less than 10% of the gene orthologs showing higher conservation of expression than the neutral expectation (p < 0.05). Of importance, searching this database for LG1 expression showed that this gene was not mutually expressed in mouse and human kidney (doi.org/10.1371/journal.pone.0046876).

In summary, hyponatremia is a distinguished feature of anti-LGI1 antibody encephalitis. The pathogenesis is most
probably SIADH due to an immune response targeting the LGI1 protein in the hypothalamus. Symptomatic hyponatremia secondary to SIADH is a common clinical problem and may delay the correct diagnosis of encephalitis. Hypomagnesemia and hypophosphatemia are additional clues to the correct diagnosis. Awareness of this association among neurologists and non-neurologists may assist in identifying and treating this condition.

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Disclosure
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Appendix

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<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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</thead>
<tbody>
<tr>
<td>Avi Gadoth, MD</td>
<td>Department of Neurology, Encephalitis center, Tel-Aviv Medical Center, Sacker School of Medicine, Tel Aviv University</td>
<td>Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data</td>
</tr>
<tr>
<td>Michal Nisbonyam Ziv, MD</td>
<td>Department of Neurology, Sourasky Tel Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Major role in the acquisition of data; study concept or design; analysis or interpretation of data</td>
</tr>
<tr>
<td>Yifat Alcalay, PhD</td>
<td>Encephalitis center, Immunology laboratory, Sourasky Tel Aviv Medical Center</td>
<td>Major role in the acquisition of data; analysis or interpretation of data</td>
</tr>
<tr>
<td>Asia Zubkov, MD</td>
<td>Department of Pathology, Tel Aviv Medical Center, Sacker School of Medicine, Tel Aviv University</td>
<td>Major role in the acquisition of data; analysis or interpretation of data</td>
</tr>
<tr>
<td>Idit Schwartz, MD</td>
<td>Department of Nephrology, Sourasky Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Analysis or interpretation of data</td>
</tr>
<tr>
<td>Doron Schwartz, MD</td>
<td>Department of Nephrology, Sourasky Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Analysis or interpretation of data</td>
</tr>
<tr>
<td>Mariana Abboud, MSc</td>
<td>Oncology Division, Sourasky, Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Major role in the acquisition of data; analysis or interpretation of data</td>
</tr>
</tbody>
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References

19. Rubinek, PhD Tamar Yocsopowitch, MD Ofer Schwartz, MD Talia Weinstein, MD, PhD

Appendix (continued)

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</tr>
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<tr>
<td>Tamar Rubinek, PhD</td>
<td>Oncology Division, Sourasky, Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data</td>
</tr>
<tr>
<td>Ofer Yosselwitsch, MD</td>
<td>Department of Urology, Sourasky, Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Major role in the acquisition of data; analysis or interpretation of data</td>
</tr>
<tr>
<td>Talia Weinstein, MD, PhD</td>
<td>Department of Nephrology, Sourasky, Tel-Aviv medical center, Sacker School of Medicine, Tel Aviv University</td>
<td>Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data</td>
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