

Case report

A rare case of proliferative glomerulonephritis with monoclonal IgG deposits in an adolescent female; mimicking immune complex glomerulonephritis, (When & Where??)

Abstract: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare renal disease under the spectrum of monoclonal gammopathy of renal significance (MGRS). Majority of the cases have been diagnosed in adult population, especially after the age of 40 years. We report a rare case of PGN(MID) in a 16 years old female, presented with nephrotic syndrome and active urine sediment. She had normal serum creatinine, low C3 and negative infective and autoimmune markers. Renal biopsy revealed membranoproliferative glomerulonephritis (MPGN) with monoclonal IgG3 kappa deposits. Our adolescent patient was treated with standard antiproteinuric therapy and steroid. Though C3 became normal on follow up, but proteinuria was increased and rituximab was added. Our case emphasizes the awareness by nephrologist and renal pathologist about this rare disorder even in adolescent population for accurate diagnosis, prognostication and treatment.

Keywords: Proliferative glomerulonephritis with monoclonal IgG deposits, membranoproliferative glomerulonephritis, IgG3 kappa

Introduction:

Monoclonal gammopathy of renal significance (MGRS) is a recently described term that encompasses several diseases. It is defined as a clonal proliferative disorder producing nephrotoxic monoclonal immunoglobulin that does not meet criteria for treatment of a specific malignancy or infection (1). The spectrum of MGRS is broad, and glomerulonephritis are featured either by organized or non-organized deposits (2,3). In 2004, Nasr et al. described a unique form of glomerular injury associated with monoclonal IgG deposition, which was termed "proliferative glomerulonephritis with monoclonal IgG deposits" (PGNMID) (4). Majority of the patients with this rare disease present with deranged renal function, nephrotic range proteinuria or nephrotic syndrome. Most common histopathological pattern being MPGN pattern of injury. PGNMID is featured by glomerular monoclonal IgG deposits and glomerular deposits by electron microscopy (EM)(4, 5). To date, most cases has been described in older population over 40 years (5,6).

Here, we describe a case of PGNMID in a young adolescent girl which mimics immune complex glomerulonephritis at its initial presentation. To the best of our knowledge, this rare entity (PGNMID) is rarely described in adolescent population specially in India. Our case may be a primary trigger to broaden the epidemiological understanding of this rare glomerular disease and to include this as a differential diagnosis in appropriate clinical setting even in adolescent population.

Case Presentation:

A 16-year-old female with known hemoglobin E disease initially presented to our institute with complaints of occasional pedal swelling, facial puffiness, arthralgia, cramps in legs, photosensitivity, decreased appetite, hair fall, frothy urine with reddish discoloration of urine for last 6 months with preserved urine output. Her physical examination was remarkable for severe pallor, 2+ lower extremity edema, blood pressure of 110/70 mmHg and urine dipstick finding of protein 3+ and blood moderate. Systemic examination was unremarkable. Her initial laboratory evaluations demonstrated a serum creatinine level of 0.97 mg/dl, Hb 6.6 g/dl, 24-hour urine protein measuring 7 gm, urine routine & microscopy of protein 3+, RBC 25-30/high power field (hpf), pus cell 12-15/hpf, sterile urine culture. Serology for viral infections, including HIV, Hepatitis B, and Hepatitis C, yielded negative results. Moreover, the autoimmune panel, which included anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), anti-myeloperoxidase (MPO), anti-proteinase 3 (PR3), anti-DNA antibody, anti-glomerular basement membrane (GBM), and anti-phospholipase A2 (PLA2R) antibodies, were universally negative. Complement levels were depressed, C3 66 and C4 8.29. Other reports were serum calcium of 8.6, PO4 5.1, uric acid 8.3, serum total protein 4.8 g/dl, Albumin 3.1 and Globulin 1.7 g/dl, Liver Function Test- Total bilirubin 0.46 mg/dl, Direct bilirubin 0.19 mg/dl, Indirect bilirubin 0.27 mg/dl, SGOT 66 U/L, SGPT 60, ALP-normal; Lipid profile- Cholesterol 304 mg/dl, Triglyceride 682 mg/dl, HDL 99 mg/dl, LDL 69 mg/dl, VLDL 136 mg/dl. Serum cryoglobulin titer was negative. Diagnostic imaging through ultrasound revealed normal study and 2D echocardiography revealed LVEF 60%. She was started on oral Prednisolone 1 mg/kg on suspicion of immune complex glomerulonephritis. ANA was repeated on strong suspicion of Lupus nephritis but it was repeatedly negative. She underwent renal biopsy, which revealed membranoproliferative glomerulonephritis pattern (MPGN) without tubulointerstitial chronicity on light microscopy findings. Direct immunofluorescence (DIF) revealed IgG: 3+ granular mesangial and peripheral capillary wall deposit, IgA: Negative, C3c: 2+ granular mesangial and peripheral capillary wall deposit, C1q: 2+ granular mesangial and peripheral capillary wall deposit, Kappa: 3+ granular mesangial and peripheral capillary wall deposit, Lambda: negative; and Electron microscopy revealed intramembranous and subendothelial electron dense immune complex type deposits along with GBM double contouring with interposition of mesangial cells. At this point, there was dilemma between lupus nephritis and proliferative glomerulonephritis monoclonal immunoglobulin G deposition disease (PGNMID). With low complement level, MPGN pattern in light microscopy and subendothelial electron dense deposits, lupus nephritis was a possibility but Kappa restriction, and possible similar light microscopy and electron microscopy picture pointed to the possible alternate diagnosis like PGNMID. So, to clear the doubt, re-biopsy with IgG subtyping was planned.

Repeat kidney biopsy, done showed MPGN pattern of injury with IF/TA of 10-15%, DIF suggestive of IgA: Negative, IgG subclass revealed to have monoclonality, i.e., only IgG3: 2+ mesangial & capillary wall granular/confluent, IgM Negative, C3: Negative, C1q: 2+ mesangial & capillary wall granular/ confluent, Kappa light chains: 2+ mesangial & capillary wall granular/confluent and Lambda light chains: Negative.

In view of the biopsy report with IgG subtyping, diagnosis of PGNMIID was confirmed. Hence, prednisolone was gradually tapered and stopped. Later, Serum protein electrophoresis with immunofixation was done which revealed no M band. Bone marrow biopsy revealed 3% plasma cells and reactive marrow, no abnormal cells identified. Subsequent C3/C4 were 94/21.5 i.e. within normal range. She was started on anti-proteinuric agents like Telmisartan and Dapagliflozin but due to uncontrolled proteinuria, was decided to start on Injection Rituximab. She was administered 4 doses of Rituximab @375 mg/m² on weekly intervals in April, 2024 without any adverse event and being followed up to evaluate response.

Table 1: Lab investigations

	August 2023	September 2023	December 2023	March 2024	NORMAL REFERENCE VALUES
Hemoglobin (g/dl)	6.6		8.8	5.1	12-16 g/dl
MCV/MCH (fl/pg)	61.5/ 19.8				80-100 fl, 27-31 pg
Urea (mg/dl)	51 mg/dl		26	36	18-55 mg/dl
Creatinine (mg/dl)	0.97		1	2.26	0.7-1.2 mg/dl
Na(mEq/L)	137.5		142	141	136-145
K (mEq/L)	3.47		4.2	4.95	3.5-5.1
Ca/PO4 (mg/dl)	8.6/ 5.1		9.1/4.8	8.4/6.2	8.8-10.2/ 2.6-4.5
Total Bilirubin (mg/dl)	0.46		0.2	0.29	0.1-1.2
Direct/Indirect bilirubin (mg/dl)	0.19/0.27				0 -0.3; 0.2-0.8
Albumin/Globulin (g/dl)	3.1 /1.7 g/dl		2.8/1.8	2/2.1	3.5-5.5; 2.3-3.4
AST/ALT (U/L)	66 / 60 U/l		20/ 09	21/9	5-40; 7-56
ALP (U/L)			47	75	44-147
T. Cholesterol (mg/dl)	304		382	386	<200 mg/dl
Triglyceride (mg/dl)	682		243	434	< 150 mg/dl
LDL (mg/dl)	99		256	238	60-130 mg/dl
HDL (mg/dl)	69		77	61	>40 mg/dl
VLDL (mg/dl)	136		49		<30 mg/dl
Ferritin (ng/ml)			191	124	13-150 ng/ml
Urine Routine & Microscopy	Protein 3+, RBC 25-30/hpf, pus cell 12-15/hpf			Protein 3+, RBC 0-1/hpf pus cell 2-3/hpf	Protein nil, RBC 0-3/hpf, pus cell 0-5/hpf
Urine Culture	No growth				
24-hour urine Protein	7 gm (urine volume 1 litre)			8 gm (volume 1.5 L)	<150 mg/day
C3/ C4 (mg/dl)	66/8.29	83.3/ 13.3	94/ 21.5	89/20.5	90-180; 10-40
ANA/ANA profile/ ANCA/MPO/PR3/ PLA2R/ anti GBM	All Negative	All Negative	All Negative	All Negative	MPO <20 RU/ml, PR3 <20 RU/ML, <20 RU/ML; ANTI GBM <20 RU/ML
S. Cryoglobulin	Negative				
SPEP with Immunofixation			No M Band seen		

HBsAg, anti HCV, HIV 1 & 2	Non-reactive			Non-reactive	
Bone Marrow Biopsy			Plasma cell 3%, reactive marrow, abnormal cells not seen		
2D-Echocardiography	LVEF 60%			LVEF 62%, No RWMA, No PE	
Ultrasonography abdomen	Normal study			Normal Study	
Chest X ray	Normal study			Normal Study	

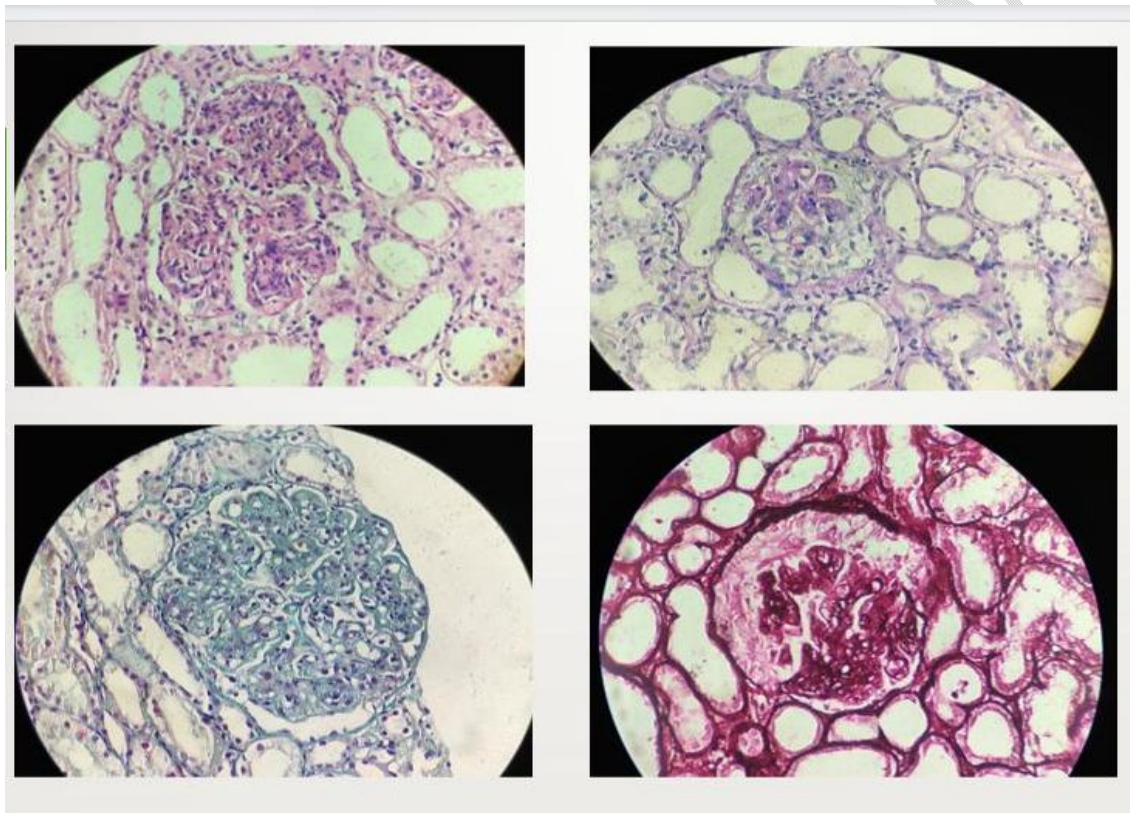


Figure 1. Kidney Biopsy (29/8/23): Light Microscopy: Left Upper picture: H & E stain showing lobular accentuation, polymorphonuclear infiltration, Right upper picture: PAS stain showing Crescent, Left down picture: Methyl Trichrome showing GBM double contour and subendothelial fuscinophilic deposits, also lobular accentuation and polymorphonuclear infiltration visible, Right Down picture: JMS showing circumferential cellular crescent.

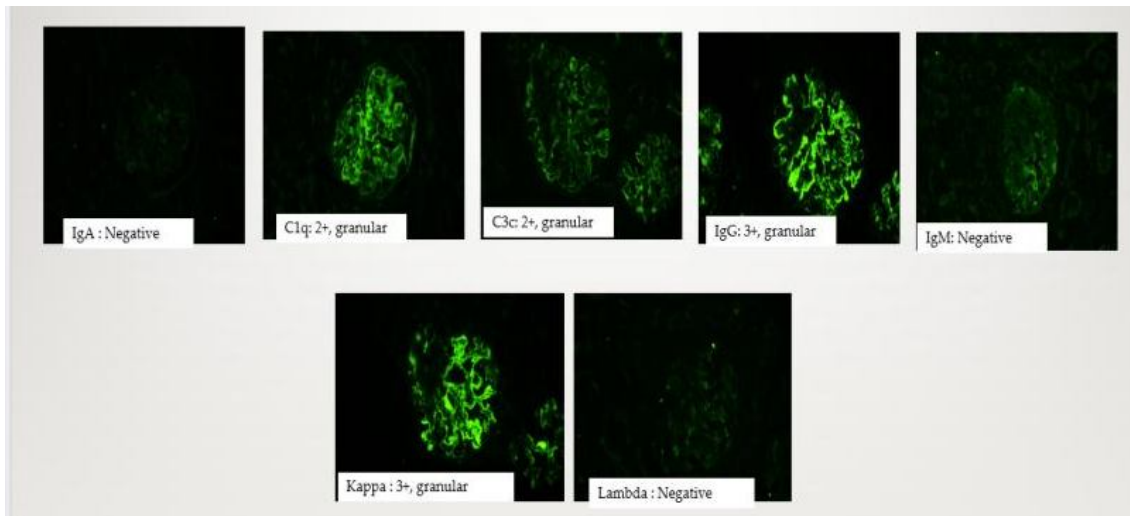


Figure 2: Kidney Biopsy (29/8/23): Immunofluorescence showing IgA: Negative, C1q: 2+ granular mesangial and peripheral capillary wall deposits, C3c: 2+ granular mesangial and peripheral capillary wall deposits, IgG: 3+ granular mesangial and peripheral capillary wall deposit, IgM: Negative, Kappa: 3+ mesangial and peripheral capillary wall deposits, Lambda: Negative

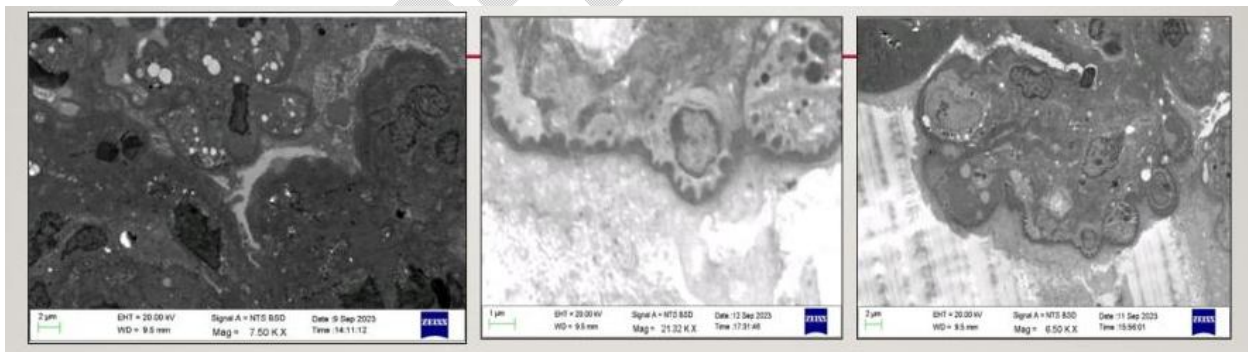


Figure 3: Kidney Biopsy (29/8/23): Electron Microscopy: Electron dense subendothelial and intramembranous deposits present along with GBM double contouring with interposition of mesangial cells.

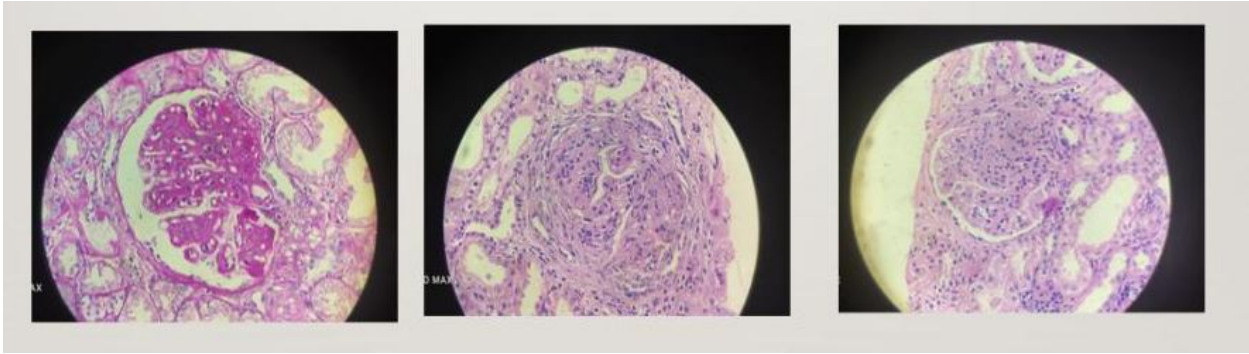


Figure 4. Repeat Kidney Biopsy (25/9/23): Light Microscopy: Extreme Left picture: PAS stain showing lobular accentuation, segmental double contouring of GBM, wire loop lesions, Middle picture: H & E stain showing Crescent, Extreme Right picture: H & E showing endocapillary hypercellularity, lobular accentuation and polymorphonuclear cell infiltration.

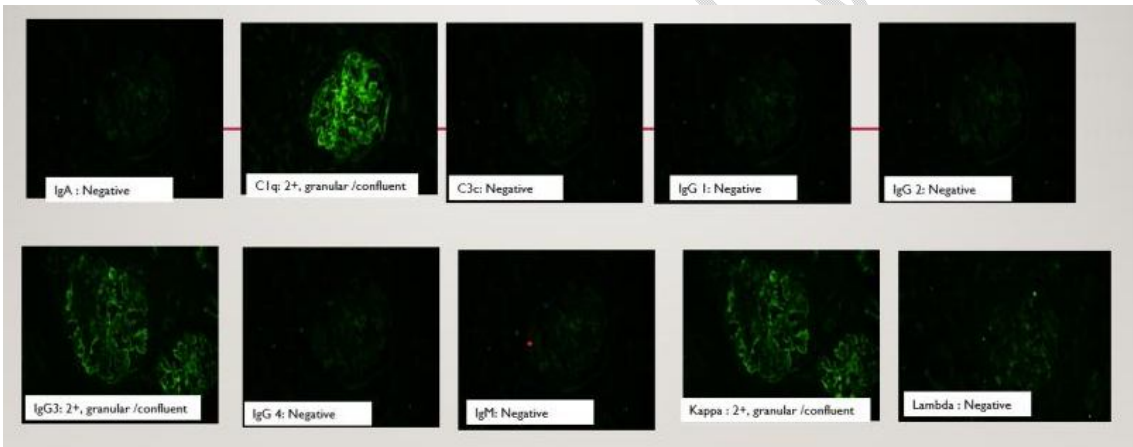


Figure 5: Kidney Biopsy (25/9/23): Immunofluorescence with IgG subtype showing IgA: Negative, C1q: 2+ granular/confluent mesangial and peripheral capillary wall deposits, C3c: Negative, IgG1 subclass: Negative, IgG2 subclass: Negative, IgG3 subclass: 2+ granular/ confluent mesangial and peripheral capillary wall deposit, IgM: Negative, Kappa: 2+ granular/confluent mesangial and peripheral capillary wall deposits, Lambda: Negative

Discussion:

PGNMID is a recently described entity among the spectrum of monoclonal gammopathy of renal significance (MGRS). It is reported that the renal biopsy incidence of PGNMID is only about 0.17% (5). Clinically, this disease is renal limited and manifests with chronic glomerular disease, altered renal function and albuminuria, sometimes in the nephrotic range. Acute nephritic syndrome is rare. PGNMID affects mostly adults more than fifth decade but can affect younger adults and adolescents too. Histologically, PGNMID is characterized predominantly by membranoproliferative GN and less frequently by diffuse endocapillary GN, mesangio-proliferative GN or atypical membranous deposits. Immunofluorescence and

electron microscopic studies are the cornerstone of diagnosis, showing granular deposits involving glomeruli only, and composed of monotypic immunoglobulin G (IgG), with a single heavy chain subclass (most commonly IgG3) and light chain (LC) restriction (usually K), admixed with complement deposits. Ultra structurally, deposits are amorphous and involve predominantly subendothelial and mesangial distribution. PGNMID should be distinguished from type 1 cryoglobulinemic GN and immunotactoid GN, which share some common pathologic features. Approximately 70% of cases do not have detectable blood or bonemarrow monoclonal immunoglobulins (7). Thus, many PGNMID cases might not detect monoclonal immunoglobulins. PGNMID is differentiated from membranoproliferative glomerulonephritis resulting from immunocomplexes (eg, lupus nephritis, chronic infections) by serology and by kidney biopsy because there is polyclonal staining of deposits (ie, both k and l) in the latter. The rarity of this disease entity is limiting factor to establish standard treatment guideline. Multiple therapies including standard antiproteinuric agents, steroid, rituximab and other immunosuppressive drugs have been tried with variable results.

Conclusion: We describe PGNMID in a 16 years old adolescent female. Presentation of such a rare disease in this atypical age group is rarely reported in literature especially in Indian sub-continent. Our case may be an eye opener for nephrologist and renal pathologist to consider PGNMID even in adolescent and young population in appropriate clinical setting. Multicenter studies are required to guide and establish standard diagnostic algorithm and treatment approach.

References:

1. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the international kidney and monoclonal gammopathy research group. *Nat Rev Nephrol.* 2019;15(2):121. <https://doi.org/10.1038/s41581-018-0102-7>
2. Bridoux F, Leung N, Hutchison CA, et al. Diagnosis of monoclonal gammopathy of renal significance. *Kidney Int.* 2015;87(4):698–711. <https://doi.org/10.1038/ki.2014.408>
3. Kanzaki G, Okabayashi Y, Nagahama K, et al. Monoclonal immunoglobulin deposition disease and related diseases. *J Nippon Med Sch.* 2019;86(1):2–9. https://doi.org/10.1272/jnms.JNMS.2019_86-1
4. Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. *Kidney Int.* 2004;65(1):85–96. <https://doi.org/10.1111/j.1523-1755.2004.00365.x>
5. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol.* 2009;20(9):2055–64. <https://doi.org/10.1681/ASN.2009010110>
6. Guiard E, Karras A, Plaisier E, Duong Van Huyen JP, Fakhouri F, Rougier JP et al. Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab. *Clin J Am Soc Nephrol.* 2011 Jul;6(7):1609–16. doi: 10.2215/CJN.10611110. Epub 2011 Jun 23
7. Noto R, Kamiura N, Ono Y, Tabata S, et al. Successful treatment with bortezomib and dexamethasone for proliferative glomerulonephritis with monoclonal IgG deposits in multiple myeloma: a case report. *BMC Nephrol.* 2017;18:127. doi: 10.1186/s12882-017-0524-7