INVITED COMMENTARY

Hypertension in Nephrotic Syndrome: A Pressing Concern

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High blood pressure is often detected in patients with nephrotic syndrome, at the onset of the illness, following therapy with prednisolone, and/or during long-term follow-up. A review of cardiovascular outcomes in proteinuric glomerulopathies showed that the prevalence of hypertension ranges from 7% to 41% in steroid sensitive nephrotic syndrome, compared to 13% to 58% in patients with steroid resistance [1]. In patients with steroid sensitive disease, high blood pressure was found in 65% to 95% of patients with edema, which persisted in 19% to 34% following steroid induced remission [2,3]. The prevalence of hypertension is highest in patients with frequent relapses or steroid dependence, and in those with family history of essential hypertension [1,3]. Masked hypertension, which is in itself associated with adverse cardiovascular outcomes, is reported in 16% to 40% of such patients. [4,5]

Hypertension in nephrotic syndrome may be attributed to intrinsic renal and non-renal causes, as well as extrinsic reasons. The chief renal causes include primary salt and water retention, fluid overload, glomerulosclerosis related decline in glomerular filtration rate, and proliferative glomerulonephritis. Important extrarenal factors contributing to hypertension are therapy with corticosteroids or calcineurin inhibitors, and dyslipidemia [1]. Hypertension has long-term cardiovascular consequences, including left ventricular hypertrophy and atherosclerosis, and leads to end-organ injury, such as retinopathy and progressive kidney disease. Almost one-third of children with primary hypertension show echocardiographic evidence of left ventricular hypertrophy, underscoring the importance of detection and appropriate management of hypertension in children [6].

A prospective single-center observational study, published in this issue of the *Journal* [7], aimed to evaluate the prevalence of hypertension in 83 children with infrequently relapsing nephrotic syndrome during a relapse and following 4-weeks of prednisolone therapy. The authors also evaluated if hypertension was associated with family history, dyslipidemia, or end organ damage. Blood pressure was measured in the clinic as the mean of three recorded values, and hypertension was defined as per standard guidelines [8]. The authors found that almost one-third (32.5%) of patients had hypertension during disease relapse, which persisted in one-quarter of cases (8.6%) following 4-weeks of prednisolone therapy. Amongst hypertensive patients, 29% had a family history of hypertension, and ~50% had history of hypertension at disease onset or during a previous relapse. While a proportion of patients showed abnormal left ventricular geometry, concentric left ventricular hypertrophy was uncommon. These findings are noteworthy, since clinic hypertension was found in ~30% patients with active disease, compared to an estimated population prevalence of ~4% for primary hypertension [9]. However, it would be important to emphasize few issues of relevance for practicing clinicians and researchers.

The eligibility criteria state that inclusion was limited to patients who were receiving antihypertensive medications for 3-months or longer. In order to determine the prevalence of hypertension in infrequent relapsers, it would have been appropriate to include all patients with infrequent relapses, irrespective of antihypertensive therapy. While the use of antihypertensive medications might have led to underestimation of the prevalence of hypertension, the true prevalence might indeed have been lower were all the patients with infrequent relapses included. Secondly, patients with hypertension appear to have had more severe relapses, as indicated by serum and urine biochemistry. A prolonged duration of disease and delayed therapy of relapse might influence the severity of relapse and result in hemodynamic aberrations, including hypertension. Thirdly, in order to negate the influence of corticosteroid therapy on hypertension, repeat blood pressure values should have been estimated a few months remote from the relapse. Further, the value of detecting transient hypertension is uncertain, since persistent hypertension is more likely to correlate with cardiovascular outcomes than acute hypertension associated with a relapse compared to casual clinic blood pressure records, ambulatory blood pressure monitoring (ABPM) is a comprehensive technique to detect

abnormal blood pressure in adults and children [10]. Its advantages include reproducibility, better correlation with end organ injury, and cost-effectiveness. ABPM is optimal in diagnosing and confirming high blood pressure records, white coat hypertension and masked hypertension, and helps optimize antihypertensive medications [10]. Its application in children is currently limited by availability of child validated equipment, and lack of normative data that reflects racial and ethnic diversity [8]. However we emphasize that prospective studies to classify and determine the true prevalence of hypertension should ideally be based on ABPM. In absence of ABPM, home blood pressure measurements using oscillometric devices have been advocated. However, the sensitivity, specificity and positive and negative predictive values of home measurements are rather modest, when compared to ABPM [11]. Expert groups therefore suggest using home blood pressure monitoring as an adjunct to casual blood pressure and ABPM following the diagnosis of hypertension.

In conclusion, findings of this and other reports suggest that acute but transient hypertension is common during relapses of steroid sensitive nephrotic syndrome. Prospective studies on prevalence of hypertension should have broad-based inclusion criteria and avoid confounders that might affect outcomes. It is necessary to follow up these patients, preferably when in remission and off corticosteroids, to determine if hypertension indeed persists and determine risk(s) for adverse cardiovascular outcomes.

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