Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation

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Background. Intrauterine growth retardation (IUGR) is associated with higher morbidity and mortality not only in perinatal life but also in later life. The purpose of our study was to determine whether IUGR has any effect on the course of minimal change nephrotic syndrome (MCNS) in children.

Methods. Forty children who were between 1 and 16 years old at the onset of MCNS, who have been followed for at least three years and for whom we were able to obtain birth weights and gestational ages, were included. The diagnosis of MCNS was predicted on the basis of clinical and laboratory features, and in 11 children (27.5%) the diagnosis was confirmed by renal biopsy. IUGR was defined as birth weight below the tenth percentile for gestational age.

Results. Five children (12.5%) had signs of IUGR at birth. In children with IUGR, we observed a higher mean number of relapses (10.4 vs. 3.3, P < 0.001) and a higher incidence of steroid dependency (80% vs. 21%, P < 0.02) than in children without IUGR. Other differences between children with and those without IUGR included more frequent treatment with cytotoxic agents and cyclosporine, and a higher incidence of renal biopsy in children with IUGR.

Conclusion. Our study demonstrated an unfavorable course of MCNS in children with IUGR. IUGR could therefore enable early identification of those children who are at risk of becoming frequent relappers and of developing steroid dependency. This, however, should be confirmed in a larger number of patients.

METHODS

Patients

Our study included children between 1 and 16 years of age with MCNS referred to the Pediatric Hospital in Ljubljana between 1984 and 1993. At least three-year follow-up was thus possible.

Nephrotic syndrome was defined as proteinuria > 40 mg/m²·hr, plasma albumin < 25 g/liter, and the presence of edema and hyperlipidemia. Diagnosis of MCNS was predicted on the basis of clinical and laboratory features [12]. Renal biopsy was performed in children who did not respond to initial treatment with corticosteroids, who had frequent relapses, and/or who had initial hematuria. Corticosteroid resistance and dependency, as well as remission and relapse were defined according to the generally accepted criteria [12, 13].

Initial attack and relapses were treated by methylprednisolone 0.8 to 1.2 mg/kg per day until remission plus one week, followed by alternate-day methylprednisolone of 1 mg/kg per 48 hours for four more weeks.

Birth weights and gestational ages were obtained from the records of the Slovene maternity hospitals and from the records of the pediatric files. IUGR was defined as birth weight below the tenth percentile for gestational age.
used the growth rate curves for single births in Slovenia [14].

The study was approved by the State Ethical Committee.

Statistical analysis

Numerical variables were analyzed by Student’s t-test; if the distribution of values within the variables was not normal, the Wilcoxon test was applied. Attributional variables were analyzed by Fisher’s exact test. Differences were considered to be statistically significant at $P \leq 0.05$.

RESULTS

During a 10-year period, 42 patients with MCNS were treated at the Pediatric Hospital in Ljubljana. Two children with MCNS were not included in the study because we were not able to obtain their birth weights.

Among the 40 children included in our study, 16 were girls and 24 were boys, aged 14 months to 14 years (mean 3.9 years). In 11 patients (27.5%), the diagnosis of MCNS was confirmed by renal biopsy (in 3 of 5 children with IUGR, and in 8 of 35 children without IUGR, $P = 0.08$).

Patients’ birth weights and gestational ages

Five of the 40 children with MCNS (12.5%) had signs of IUGR at birth. Their birth weights ranged from 1940 g to 3000 g (mean 2528 ± 410), and they were born between the 36th and 42nd weeks of gestation. The remaining 35 patients (87.5%) had no signs of IUGR at birth, their birth weights ranged from 2500 to 4200 g (mean 3446 ± 438), and they were born between the 36th and 42nd weeks of gestation.

Children with IUGR were of similar age at the onset of MCNS (5.8 ± 4.5 vs. 5.8 ± 3.8, NS), and have been followed for a similar period (6.4 ± 1.1 vs. 6.1 ± 2.7, NS) as children without IUGR.

Treatment of nephrotic syndrome and response to treatment with corticosteroids

In two children, no specific treatment of the nephrotic syndrome was necessary because spontaneous remission occurred. The remaining 38 patients were treated with corticosteroids (Tables 1 and 2). The initial treatment with corticosteroids induced remission within four weeks in all but one patient, and all patients remained steroid-responsive throughout the course of the MCNS. In the child who did not respond to corticosteroids, remission was achieved after treatment with cyclosporine. In the subsequent course, 11 children (28.9%) developed signs of steroid dependency. Additionally to corticosteroids, treatment with cytotoxic drugs was indicated in 14 (35.0%) children and with cyclosporine in 4 children (10.0%).

Comparison between children with and those without IUGR revealed statistically significant differences in the incidence of steroid dependency ($P < 0.02$) and in the incidence of treatment with cytotoxic drugs ($P < 0.05$). Other differences between the two groups of children were not statistically significant.

Frequency of relapses

Children were followed for 3 to 11 years (mean 6.1 ± 2.6). Thirteen of the 40 children (32.5%) had no relapses (Table 3). The remaining 27 children (67.5%) followed a relapsing course, with 1 to 16 relapses (mean 4.2 ± 4.5).

Comparison between children with and those without IUGR revealed a statistically significant difference in mean number of relapses (10.4 vs. 3.3, $P < 0.001$). Other differences between the two groups of children were not statistically significant.

Frequency of complications of the nephrotic syndrome and of concomitant diseases

In all but two children, the initial attack and/or the majority of relapses, if present, were associated with upper
who are more likely to have frequent relapses and to develop steroid dependency observed in these children. Other differences between children with and those without IUGR include more frequent treatment with cytotoxic agents and cyclosporine, and a higher incidence of respiratory tract infections or bronchopneumonia. Arterial hypertension was transient in all patients and tended to be more frequent in children with IUGR than in those without IUGR. Comparison between children with and those without IUGR did not reveal any significant differences in the frequency of important complications of the nephrotic syndrome and in the frequency of concomitant diseases.

**DISCUSSION**

The results of our study indicate that IUGR predicts an unfavorable clinical course of MCNS in children. Children with MCNS who had had signs of IUGR at birth have had a significantly higher mean number of relapses than children without IUGR. Furthermore, a significantly higher percentage of children with IUGR developed steroid dependency. Other differences between children with and those without IUGR include more frequent treatment with cytotoxic agents and cyclosporine, and a higher incidence of renal biopsy in children with IUGR. More aggressive treatment and a higher incidence of renal biopsy in children with IUGR are probably due to more frequent relapses and steroid dependency observed in these children.

The ability to predict the course and outcome in children with MCNS may have significant therapeutic implications. Previous attempts to correlate the course and outcome of MCNS with the clinical, laboratory, and histologic characteristics have met with only limited success [15–18]. The best predictive value has been demonstrated for the number of relapses during the first six months [17, 18] and the characterization of the initial response to corticosteroids [18]. Our study has demonstrated a good predictive value for IUGR also, which could help to identify those children who are more likely to have frequent relapses and to develop steroid dependency even earlier in the course of MCNS. However, these conclusions should be drawn with caution as our study included a rather small number of patients with MCNS. Furthermore, it must be emphasized that the diagnosis of MCNS was confirmed by renal biopsy only in 11 children; in the remaining 29 children it was predicted on the basis of the clinical and laboratory features [12].

The results of our study provide further support for a recent hypothesis that IUGR with subsequent low birth weight for gestational age might be one of the non-immune mechanisms affecting the clinical course and prognosis of renal diseases [9–11]. Previous studies have demonstrated that patients with diabetes mellitus who had had signs of IUGR at birth are at increased risk of the development of diabetic nephropathy [19, 20]. Furthermore, in 12 patients with idiopathic membranous nephropathy, a strong correlation has been found between the patients’ birth weights and the slopes of the reciprocal creatinine regression lines [21]. Finally, we have found a higher incidence of arterial hypertension and glomerulosclerosis in children with IgA glomerulonephritis who had suffered from IUGR, than in children with IgA glomerulonephritis without IUGR [22].

The effect of IUGR on the clinical course of some renal diseases, such as IgA glomerulonephritis and diabetic nephropathy, can be explained by the low number of nephrons. Namely, it has been demonstrated that children [23] and experimental animals [24] with IUGR have a lower number of nephrons (glomeruli) than those without IUGR. Furthermore, our preliminary study revealed a lower glomerular density in individuals with low birth weight [25]. Individuals with a low number and a lower density of nephrons (glomeruli) have a diminished renal functional reserve and are therefore at higher risk of progression of renal diseases [9–11]. However, this mechanism does not explain the effect of IUGR on the clinical course of MCNS. The effect of IUGR on the clinical course of MCNS could be related to a higher morbidity described in children with IUGR [1], although we haven’t observed any significant differences in the frequency of concomitant diseases and complications of the nephrotic syndrome between children with and those without IUGR. It is therefore possible that IUGR not only results in a reduction of the total number of nephrons, but also in other changes in the morphology and/or physiology of the developing kidney, which are still poorly understood.

In conclusion, our study demonstrated an unfavorable clinical course of MCNS in children with IUGR. IUGR could therefore enable early identification of those children with MCNS who are at risk of becoming frequent relapsers and of developing steroid dependency. These findings, however, should be confirmed in a larger number of patients.
REFERENCES


