ORIGINAL ARTICLES

ANTERIOR ISCHEMIC OPTICAL NEUROPATHY IN CHILDREN ON CHRONIC PERITONEAL DIALYSIS: REPORT OF 7 CASES

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♦ **Background:** Anterior ischemic optic neuropathy (AION) is characterized by infarction of the optic nerve head due to hypoperfusion of the posterior ciliary arteries and causes sudden blindness in adults on chronic dialysis, but has rarely been described in children. Unlike adults, children do not have comorbidities related to aging.

♦ **Methods:** We retrospectively analyzed data of 7 children on nocturnal continuous cycling peritoneal dialysis (CCPD) who developed AION identified within the Italian Registry of Pediatric Chronic Dialysis. We also summarized data from 10 cases reported in the literature.

♦ **Results:** Our 7 patients suffered from acute onset bilateral blindness. Their mean age was 3.2 years and chronic hypotension had been observed prior the AION in 3 of the 7 children. Low systolic blood pressure (SBP) was associated with higher risk of developing AION according to statistical analysis. None recovered completely. In total, 11 out of 16 experienced a partial recovery and no clear evidence emerged favoring specific treatments.

♦ **Conclusions:** Hypotensive children treated with CCPD are at increased risk of developing AION, which often results in irreversible blindness.

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KEY WORDS: AION; anterior ischemic optic neuropathy; dehydration; hypotension; peritoneal dialysis; sudden blindness; young children.

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Anterior ischemic optic neuropathy (AION) has been reported as a cause of sudden visual loss in adults on chronic dialysis (1–4) but has rarely been described in children. Anterior ischemic optic neuropathy is characterized by infarction of the anterior segments of the optic nerve. Current evidence suggests that this condition is caused by an abrupt decline in the perfusion pressure of the posterior ciliary arteries, which ensures most of the blood supply to the head of the optic nerve (5). In adults, AION generally presents as an isolated, mostly monolateral event, occurring in aged patients with chronic atherosclerotic lesions. Patients on hemodialysis, exposed to large blood pressure changes, are more prone to develop AION during or immediately after hemodialysis (5). After the onset of blindness, funduscopy shows swelling of the optic disk and flame hemorrhages (6,7).

Unlike adults, children do not have comorbidities related to aging and, in this age group, AION is an exceptional event. Since 1999, 10 cases of AION in children treated with chronic peritoneal dialysis (PD) have been reported in the literature (8–11). Here, we report on 7 additional cases that have been identified within the Italian Registry of Pediatric Chronic Dialysis.

SUBJECTS AND METHODS

DATA COLLECTION

Patients with acute episodes of blindness were identified by a retrospective analysis of the Italian Registry of Pediatric Chronic Dialysis database, which has collected data on more than 700 patients since 1988. Data on all

patients, regardless of dialysis modality, were investigated. Centers that had treated these patients were then contacted and asked to retrospectively retrieve data from the medical records. In some cases, families were been contacted to collect missing data.

Blood pressure values were expressed as absolute values, percentiles, and as standard deviation score (SDS) using reference values for age, gender, and height (12,13). To identify risk factors for AION, we compared AION patients with age-matched continuous cycling peritoneal dialysis (CCPD) children taken from the Italian Registry of Chronic Pediatric Dialysis in a 1:4 ratio (AION:controls). Parameters considered were gender, age at start of dialysis, age at AION, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

STATISTICAL ANALYSIS

Data were analyzed with SPSS 11.5.1 for Windows software (SPSS Inc., Chicago, IL, USA). When indicated, data between groups (AION:controls) were compared with the Mann-Whitney U test and Fisher's exact test. Data were expressed with interquartile range (IQR). Age-matched SBP and DBP were expressed with SDS.

DATA SUMMARY

Case 1: This 26-month-old boy started CCPD at the age of 13 months for end-stage renal disease (ESRD) secondary to posterior urethral valves associated with renal dysplasia and grade IV-V reflux; he also had congenital hydrocephalus (not surgically corrected) and mild/moderate mental retardation. On PD, he was chronically hypotensive (45 – 60/30 – 45 mmHg) (SBP and DBP < 50th percentile) despite oral salt supplementations and addition of sodium chloride in the dialysis solutions. The child complained abruptly of visual loss while at home, early in the afternoon; his mother also noticed his pupils were dilated. Blood pressure (BP) was 62/35 mmHg (SBP and DBP < 50th percentile). Upon admission, he had fixed dilated pupils, bilaterally unresponsive to light. Funduscopy showed pale optic nerve heads with retinal edema. Brain imaging, compared with previous neurological imaging, showed stable triventricular hydrocephalus and symmetrical lesions of the caudate nuclei and putamen as well as ischemic lesions of the left occipital cortex. A lumbar puncture was performed to rule out encephalitis, yielding normal results. Hemoglobin (Hb) levels were 10.2 g/dL, and other blood tests were uninformative.

Case 2: This 8-month-old girl was born with tetralogy of Fallot, duodenal stenosis, congenital hip dysplasia, clubfoot and ESRD secondary to bilateral dysplastic kidneys. She was started on CCPD at 5 months and, soon after, underwent cardiac surgery to correct her congenital heart defect, without major complications. Her BP remained in the lower normal range (60 – 70/40 – 50 mmHg) (SBP and DBP < 50th percentile) after surgery while oxygen saturation was always in the normal range. Three months later, while she was still in the

hospital, her mother noticed that her pupils had become suddenly dilated and unresponsive to light. Blood pressure was 70/43 mmHg (SBP and DBP < 50th percentile). Funduscopy showed bilateral optic nerve swelling and pallor. Brain imaging showed mild brain atrophy and bilaterally swollen optical nerve. Biological investigations were unremarkable; Hb levels were 9.8 g/dL.

Case 3: This 11-year-old boy with Joubert syndrome and cystic kidney disease had been treated with CCPD since he was 3 years old. He had always had low blood pressure (70 – 80/40 – 50 mmHg) (SBP and DBP < 50th percentile). He was admitted to hospital after a traumatic spleen laceration resulting in hemoperitoneum. Upon admission, he was anemic (Hb 6.5 g/dL), clinically unstable with a BP of 55/27 mmHg (SBP and DBP < 50th percentile). He was immediately transfused, and Hb levels rose to 11.1 g/dL; his hemodynamic status improved in the following days after correcting hypovolemia. Two weeks later, he suddenly lost his vision around mid-day. His BP was 65/33 mmHg (SBP and DBP < 50th percentile). Ophthalmic examination revealed dilated pupils, poorly reactive to light. The eye fundus showed pale and swollen optic discs; the visual evoked potentials (VEP) were severely abnormal. Brain imaging was characteristic of Joubert syndrome, but did not show evidence of ischemic lesions.

Case 4: This 3-year-old male with posterior urethral valves, renal dysplasia and vesico-ureteral reflux (VUR), was started on CCPD at the age of 28 months. Blood pressure had always been in the normal range for his height. He was admitted to the hospital for diarrhea and dehydration. After 36 hours, he became suddenly blind. Blood pressure was 90/60 mmHg (SBP and DBP 50 – 90th percentile). Ophthalmologic examination revealed complete loss of visual fixation and dilated pupils unresponsive to light. Bilateral disc pallor was observed with funduscopy. Brain imaging did not show abnormalities; Hb could not be traced back in the medical chart.

Case 5: This 8-month-old child with congenital nephrotic syndrome and neurological sequelae secondary to neonatal asphyxia had been on CCPD since the age of 5 months, after a bilateral nephrectomy. Blood pressure values were in the normal range. He was admitted to hospital with seizures. He became suddenly visually unresponsive, with dilated pupils, unresponsive to light. BP was 53/26 mmHg (SBP and DBP < 50th percentile). At funduscopy, optic discs were pale and swollen, with irregular vessels. Visual evoked potentials showed only very weak response above background signal. Brain imaging showed chronic ischemic lesions of the right temporal and left parietal areas; no acute changes were detected; Hb levels were 8.5 g/dL.

Case 6: This 3-year-old boy started PD at the age of 7 months for ESRD secondary to posterior urethral valves, VUR, and renal dysplasia. Blood pressure had always been in the normal range. Two months prior to the acute visual event, he had been admitted to hospital for cardiac failure complicated with severe

hypotension. The cause of cardiac failure was not clear. One week prior to the episode of AION, his mother independently decided to use PD solutions with higher glucose concentration to increase ultrafiltration and improve his cardiac status. The child awakened after an afternoon nap, at home, complaining of complete visual loss; his pupils were dilated and unresponsive to light. Blood pressure was 63/46 mmHg (SBP and DBP < 50th percentile). The funduscopy performed soon after at his local hospital showed bilateral optic nerve swelling and pallor with peripapillary flame hemorrhages. Brain imaging showed periventricular hyperintensity in the subcortical occipital regions; Hb was 8.9 g/dL.

Case 7: This 23-month-old boy with ESRD secondary to bilateral renal hypodysplasia and VUR started chronic PD immediately after birth. His urine output had progressively decreased, and he had become anuric and severely hypertensive at 1 year of age. He was repeatedly admitted to the hospital in the following months for hypertensive crisis (140 – 150/80 – 90 mmHg) (SBP and DBP > 97th percentile) and was found to be fluid overloaded on 2 occasions, which were complicated by seizures. In an attempt to reduce his dry weight and improve his blood pressure control, high glucose concentration PD solutions were used. At 23 months, he suddenly became bilaterally blind at night. His pupils were found to be dilated and unresponsive to light. Blood pressure was 90/60 mmHg (SBP 50 – 90th percentile and DBP 90 – 95th percentile). Funduscopy was compatible with AION. Brain imaging showed periventricular hyperintensity in the frontal

and occipital regions. Physical examination revealed him to be clinically dehydrated; his Hb levels were 9 g/dL.

The above case reports, as well as data from previous reports, are summarized in Table 1.

The mean age of our patients was 3.2 years (6/7 children were younger than 3 years), 6/7 were male and 5 had some form of neurological involvement when AION developed. All patients suffered from acute onset bilateral blindness, which developed during the daytime in 6/7 patients. In addition, 3 patients had underlying conditions causing volume depletion, such as vomiting, diarrhea, or massive hemorrhage.

Chronic hypotension had been observed prior to the AION in 3/7 children; patient 6 became hypotensive after developing heart failure. Comparison of AION patients with age-matched CCPD children taken from the Registry revealed that SBP was significantly lower in children who developed AION ($p < 0.001$). A similar trend was observed for DBP but was not statistically significant. Results of the analysis are reported in Table 2.

All our patients were treated with intravenous (IV) steroids in varying dosages. In 3 of them, oral steroids were subsequently continued. In 2 cases, retrobulbar injections of steroids were administered. Five of the 7 received fluid and salt supplementation. In 4 of the 7, the erythropoietin dosage was increased. Two patients received midodrine and 2 antithrombotic agents. Four of 7 did not recover visual acuity and 3/7 had a partial recovery. At the last follow-up, 2 patients had died.

Table 1 also summarizes data from the literature on 10 children. Their mean age was 2.7 years, without prevalence of

TABLE 1
Patient Characteristics

	Ref 8	Ref 9	Ref 10	Ref 11	Current report	N – mean	% – range
Number of patients	2	2	5	1	7	17	
General characteristics							
Mean age (years)	2.3	3.2	2.7	2.0	3.2	2.9	[0.8 – 11]
Male:Female	1:1	1:1	3:2	1:0	6:1	12:5	70:30%
Anephric	0	0	3	1	1	5/17	29%
Neurological involvement	1	0	1	0	5	8/17	47%
Underlying renal disease							
CAKUT	0	2	1	1	3	8/17	47%
Steroid resistant nephrotic syndrome	0	0	3	0	1	4/17	24%
Ciliopathy	2	0	1	0	2	5/17	29%
Blood pressure							
Chronic hypotension	2	N/A	2	1	3	8/15	53%
Clinical conditions leading to hypotension	0	0	3	1	5	9/17	53%
Low BP at onset of AION	2	1	4	1	5	13/17	76%
Characteristics of blindness							
Bilateral blindness	2	2	5	1	7	17/17	100%
Acute onset	2	2	5	1	7	17/17	100%
Onset during daylight	N/A	2	N/A	N/A	6	8/9	88%

CAKUT = congenital anomalies of the kidney and urinary tract; N/A = not available; BP = blood pressure; AION = anterior ischemic optic neuropathy.

TABLE 2
Comparison of AION Patients with Age-Matched Patients Treated with CCPD

	Units	Control patients	AION	<i>p</i>
Number of patients	N	28	7	
Gender	M:F	21:7	6:1	0.484
Age at start dialysis	Years	2.08 (IQR: 1.22; 3.14)	2.16 (IQR: 0.67; 3.07)	0.888
Time from dialysis start to AION	Years	1.10 (IQR: 0.62; 2.90)	0.70 (IQR: 0.50; 2.20)	0.614
Systolic BP	SDS	+1.18 (IQR: -0.82; +1.86)	-2.25 (IQR: -2.78; +0.24)	<0.001
Diastolic BP	SDS	+0.96 (IQR: +0.82; +2.15)	+0.15 (IQR: -0.54; +1.32)	0.066

AION = anterior ischemic optic neuropathy; CCPD = continuous cycling peritoneal dialysis; M = male; F = female; IQR = interquartile range; BP = blood pressure; SDS = standard deviation score.

gender or association with specific underlying renal diseases. Three of the 10 cases had been bilaterally nephrectomized. Nearly all the patients (8/10) were hypotensive at onset of AION and 5/8 had been chronically hypotensive. All children developed acute bilateral blindness. All reported children to date had been treated with PD, and, where specified, all were treated with CCPD.

In total, 9 of 17 (53%) patients were treated with IV hydration and salt supplementation; IV and/or oral steroids were given 13 of 17 (76%) patients with different dosages; in addition, 2 patients (12%) received retrobulbar injections of methylprednisone. Erythropoietin was started or increased in 7 out of 17 (41%) patients.

Overall, 3 patients died within 2 years of the onset of AION. Visual outcome data were available for 16 patients (1 patient died after 4 days). None recovered completely, 11 of 16 (68%) experienced a partial recovery and 5 of 16 (32%) remained blind. From the limited available data, no clear evidence emerged favoring specific treatments.

DISCUSSION

Anterior ischemic optic neuropathy is a rare but dramatic event that can occur in patients on dialysis and that causes sudden visual loss secondary to infarction of the anterior segments of the optic nerve (7). Most data come from the adult literature and indicate that hypoperfusion of the posterior ciliary arteries, which perfuse the head of the optic nerve, is the principal culprit of this condition (14,15). In general, funduscopy performed immediately after the acute symptoms shows swelling of the optic disk and flame hemorrhages (6,7,16). In most adult cases, AION presents as an isolated, monolateral event that occurs primarily in aged patients. Reported risk factors include long-standing hemodialysis, atherosclerosis, diabetes, and anemia (1–4,5,17). In this subset of patients, AION may be precipitated by excessive use of antihypertensive drugs, causing severe hypotension, or by acute blood losses causing volume depletion (5). Bilateral blindness has also been described in adults, although rarely, in particular in patients undergoing cardiopulmonary bypass or major abdominal and orthopedic surgeries complicated by massive hemorrhage (9,18–19). Taken together, these data indicate that terminal

perfusion of the optic nerve is particularly vulnerable and that AION in adults is primarily caused by acquired vascular abnormalities (atherosclerotic vasculopathy) resulting in monolateral symptoms; in some patients, prolonged hypotension may cause bilateral blindness. In the literature, only 3 adult cases on PD who developed AION have been described, and they all presented bilateral involvement (20–22). Two out of 3 were on continuous ambulatory PD (CAPD) (20,22), while PD modality was not indicated for the third one (21). Two patients were chronically hypotensive (20,21) and no acute event had been identified for one of them. Conversely, one patient was hypertensive and anemic (22). No clear conclusion can be drawn from these data. In pediatric patients, AION is extremely rare; for this reason, no specific comorbidities or predisposing factors have been recognized. To date, only 10 patients have been described (8–11), which add up to a total of 17 patients, including this case series. In Italy, chronic PD for infants was introduced in the 1980s; the Italian Registry of Pediatric Chronic Dialysis has been collecting patient data since 1988 from all pediatric nephrology divisions in the country. It is unlikely that other cases have been missed in the present report. On this basis, the incidence of AION is approximately 1% in children on PD. Conversely, according to data derived from the dialysis registry, just 1 child on HD developed visual disturbances with no discernible cause and apparently related to hypertension. In this case funduscopy was not compatible with AION.

Our 7 children and the other 10 pediatric cases on PD reported in the literature presented bilateral blindness. Interestingly, unlike hemodialysis patients, adult patients on PD also developed bilateral AION.

This may suggest a different pathogenetic mechanism for AION occurrence in the 2 dialysis modalities. Risk factors for the development of AION in PD patients have not been clearly identified. In our patients, low SBP emerged as the only parameter significantly associated with AION. The bilateralism of symptoms favors the hypothesis that systemic drop in perfusion pressure to the eye is the major determinant of AION. This is why we focused our attention on the time of day the blindness occurred. We expected blindness to be more likely early in the morning, after nighttime volume depletion with dialysis ultrafiltration but this was not the case.

Our study is limited by the fact that it is a retrospective presentation of cases with missing clinical and laboratory data (blood pressure, hemoglobin, weight) before the acute event.

In conclusion, results of the present study indicate that children treated with CCPD who are chronically hypotensive and/or present acute volume depletion secondary to diarrhea or bleeding are at increased risk of developing AION, which often results in irreversible blindness. This dramatic event is more frequent than we initially thought and deserves to be periodically discussed to look for causes and potential preventive or therapeutic options. In these patients, particular attention should be paid to factors predisposing them to intra- and extra-dialytic hypotension. High glucose concentration solutions and excessive ultrafiltration should be limited in chronic hypotensive PD patients. At least in some of them, sodium supplementation in dialysate solution is indicated. Even in patients with normal or high blood pressure values, antihypertensive drugs should be used with caution. Moreover, the most important advice is to rapidly treat clinical conditions potentially leading to hypovolemia. No clear conclusions on therapy can be drawn. Steroid treatment has been tried in most of the patients but it does not seem to have influenced recovery of visual acuity. Midodrine and antithrombotic agents have been attempted in a few patients without benefits. Those patients with brain imaging showing mild ischemic lesions or none demonstrated at least partial visual recovery.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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