Intracranial Hypertension and Papilledema in a Large Cohort of Pediatric Patients With Alagille Syndrome

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ABSTRACT

Aims and Background: Ophthalmic abnormalities are amongst the 5 major criteria required for a diagnosis of Alagille syndrome (ALGS), of which embryotoxon, pseudopapilledema, and hypopigmented retinopathy are the most common. Papilledema with or without intracranial hypertension (ICHT) is rarely described. We report 9 pediatric cases of ALGS with bilateral papilledema, 5 of which were diagnosed with ICHT.

Methods: The ophthalmic data from 85 patients with clinically and/or genetically (n = 37) proven ALGS were reviewed. The study inclusion criteria were a positive diagnosis of ALGS and availability of ophthalmic follow-up data. Ophthalmic data from 40 patients after liver transplantation (LT) for other indications were also analyzed.

Results: Nine (13.0%) of the 69 patients meeting the inclusion criteria had papilledema. The neurological and neuroimaging results in all 9 patients were normal. These 9 patients were categorized into 4 groups: a nontransplant group (n = 1), a group with pretransplant papilledema persistent after LT (n = 2), a group with papilledema occurring after LT with spontaneous resolution (n = 1), and a group with papilledema and signs of ICHT after LT (n = 5). The patients with ICHT were treated with steroids alone (n = 1) or with acetazolamide (n = 4). A ventriculoperitoneal shunt was placed in 2 of the 5 cases because of progressive visual loss. Pseudopapilledema was present in 10 additional patients (14.5%, 10/69). One (2.5%) of the 40 patients without ALGS developed papilledema after LT.

Conclusions: True ICHT may be underdiagnosed in patients with ALGS. Our findings underscore the need for close ophthalmic follow-up before and after LT in these patients.

Key Words: embryotoxon, liver transplantation, pseudopapilledema, retinopathy

An infographic is available for this article at: ***http://links.lww.com/MPG/C14***.

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What Is Known

- Papilledema is a sign of intracranial hypertension, and a neurologic evaluation is required to exclude this condition in patients with papilledema.
- Only 6 cases of intracranial hypertension have been described in patients with Alagille syndrome, and very few cases in association with papilledema.

What Is New

- We report 9 pediatric patients with Alagille syndrome and bilateral papilledema, 5 of whom were diagnosed to have intracranial hypertension after liver transplantation.
- This is the largest case series reported to date.
- We propose an algorithm of diagnosis, follow-up, and treatment for intracranial hypertension in patients with Alagille syndrome.

Alagille syndrome (ALGS) is an autosomal dominant disorder with a wide spectrum of variable severity or phenotype. The presentation predominantly involves liver disease (eg, cholestasis with jaundice, pruritus, and xanthomas) or/and heart disease, and primarily pulmonary artery stenosis. The other major signs of ALGS are a triangular-shaped face, butterfly vertebrae, and ophthalmic abnormalities (1–7). Posterior embryotoxon is the most common ophthalmic feature in patients with ALGS and is present in 78% to 95% of cases (3–5,8–10). Other ophthalmic manifestations include optic disc abnormalities (ODAs), peripheral hypopigmented retinopathy, lens opacity, hypopigmentation of the iris, and Axenfeld anomaly (8–10). Pseudopapilledema (PPO) due to papillary drusen is the most frequent ODA. These globular collections of proteins and calcium can elevate the optic disc, thus mimicking papilledema (11). In papilledema, the margins around optic nerve are blurred with obscuration of the branch vessels and the nerve is thickened. These specific aspects distinguish papilledema from PPO (12,13). In papilledema, and less commonly in PPO, the retinal nerve fibers are damaged and secondary visual loss occurs (13).

Papilledema is a sign of primary or secondary intracranial hypertension (ICHT). A neurologic and imaging evaluation is required to exclude ICHT in patients with papilledema. Primary ICHT (also known as idiopathic ICHT or pseudotumor cerebri syndrome) is diagnosed when the findings of cerebral imaging and lumbar puncture do not indicate another cause. Secondary ICHT occur when an identifiable etiology is detected (tumor, malformation, medication). ICHT is associated with major ophthalmic complications, including loss of vision (12,13).

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In this report, we describe 9 cases of papilledema in a large cohort of patients with ALGS, including 5 with proven ICHT. Papilledema with or without ICHT is rarely described as part of ALGS. Only 6 cases of ICHT have been described in patients with ALGS, and even fewer cases in association with papilledema (8,14).

METHODS

We reviewed the charts of all pediatric patients diagnosed with ALGS at 2 referral hospitals (Cliniques Universitaires Saint-Luc, Brussels, n = 75; University Hospitals Geneva, Geneva, n = 10). We collected data on manifestations of ALGS, history of liver transplantation (LT), and presence of ophthalmic manifestations. The study inclusion criteria were a positive diagnosis of ALGS and adequate ophthalmic follow-up data available. ALGS was defined either clinically by the presence of at least 3 of the 5 diagnostic criteria (eg, liver disease with bile duct paucity, a heart defect, ophthalmic abnormality, a triangular face, butterfly vertebrae) or genetically by the presence of *JAG1* or *NOTCH2* pathogenic variants (1,2,15–21). Adequate ophthalmic follow-up was defined as at least 1 ophthalmic evaluation, including fundoscopy, at the time of diagnosis of ALGS and 1 evaluation after LT, when applicable. Visual acuity was defined with the Snellen scale, which is standard in Europe.

All ophthalmic evaluations were performed by a trained ophthalmologist at pretransplant evaluation, and yearly after LT. For nontransplant patients, the evaluation was performed at the time of diagnosis. If an ODA was detected, the child was examined by a specialist in neuro-ophthalmology and by a neuropediatrician. PPO was defined as the presence of a raised optic disc with blurred edges/irregular margins and the absence of optic disc cupping. Visible or buried drusen and spontaneous venous pulsation are also considered as criteria of PPO. If a clear diagnosis could not be made based on fundoscopic finding alone, ultrasonography was used to obtain colored and autofluorescence images.

True papilledema was considered in patients with a raised optic disc when the following features were present: congestion of the disc microvasculature, dilatation and telangiectasia of the surface of the disc capillaries, hemorrhages on or adjacent to the disc, obscuration of the disc margins and of the retinal vessels, and absence of venous pulsations (22).

Idiopathic ICHT was defined according to the revised diagnostic criteria published by Friedman et al (12), which includes bilateral papilledema, a normal neurologic examination, normal neuroimaging, normal composition of cerebrospinal fluid (CSF), and an elevated lumbar opening pressure. A diagnosis of probable ICHT was made if not all 5 criteria met.

The follow-up duration was defined according to the patient age in months at the time of the most recent ophthalmic evaluation. Two groups of ALGS were defined: those with papilledema and those without any signs of papilledema.

We also reviewed the charts of 40 patients who underwent LT for indications other than ALGS. These patients were selected randomly from our LT cohort that did not have severe complications (ie, prolonged hospitalization for intensive care, severe infection, early or late liver dysfunction, severe rejection, indication for a second transplant, or posttransplant lymphoproliferative disease), to achieve a better match with the characteristics of the ALGS group. This cohort was previously used as the comparison group in other studies reported (23–25). The ophthalmic evaluation is performed per protocol for all transplanted patients in the Brussels center. The difference in frequency of papilledema was compared between the ALGS cohort and the non-ALGS cohort.

Statistical Analysis

Differences between the groups were evaluated for statistical significance in univariate analyses performed using Fisher exact test and the Mann-Whitney *U* test. All statistical analyses were performed using GraphPad Prism 6 (GraphPad Software Inc, La Jolla, CA). *P* values ≤ 0.05 were considered statistically significant. The study was approved by the local ethics committee.

RESULTS

Patient Characteristics

Eighty-five pediatric patients with clinically or genetically defined ALGS were identified. Ten were followed-up at University Hospitals Geneva and 75 at the Cliniques Universitaires Saint-Luc in Brussels. Among the 85 patients with clinically proven ALGS, 50 patients underwent genetic testing. Thirty-eight of the 50 (74%) were positive for a pathogenic variant in *JAG1*, 3 were positive for a deletion in *JAG1* and none for *NOTCH2*. Fourteen patients were excluded because of lack of ophthalmic data before or after LT. Two other patients, who received transplants at beginning of the LT program, died within a month of LT. Data for 69 patients were available for inclusion in the analysis.

Forty of the 69 patients underwent LT (58.0%), and the postoperative management was similar in all cases. Seven of these 40 patients received cyclosporine as their first-line immunosuppressive treatment and the remaining 33 received tacrolimus. The dosage of tacrolimus was adjusted to maintain a trough level of around 6 μg/mL post-LT 1 year after LT. Thirty-seven of the 69 (53%) patients were diagnosed with embryotoxon during ophthalmic evaluation or follow-up. Thirty-one of the 69 (45%) patients underwent cerebral imaging studies to exclude associated intracerebral vascular malformations. No Moyamoya abnormality was observed. For 6 of 31 (19%), a minor abnormality without consequence in the cerebral perfusion was described and considered an anatomic variant.

The patient demographics and the pre-LT and post-LT ophthalmic findings are summarized in Table 1.

Patients With Papilledema

Nine (13.0%) of the 69 patients with ALGS had papilledema. Among the 9 groups, 4 groups were identified: nontransplant patient (n = 1); patients with pretransplant papilledema persistent after LT (n = 2); patients with papilledema occurring after LT but with spontaneous resolution (n = 1); and patient with papilledema and signs of ICHT occurring after LT (n = 5). Details on these patients are presented below.

The follow-up duration was similar between the patients who did and did not have papilledema ($P = 0.42$). Papilledema tended to be more common in the patients who had undergone LT than in those who had not ($P = 0.07$). There was a statistically significant difference in the follow-up duration between the patients who underwent LT (median 109 months; interquartile range 51–145 months) and the 29 patients who did not (median 75 months; interquartile range 5–63 months; $P = 0.001$).

Nontransplant Patient (n = 1)

This patient did not undergo LT and presented with signs of papilledema, despite normal neurological and neuroimaging findings. No lumbar puncture was performed. The signs of papilledema resolved rapidly in this patient, with no later recurrence.

Patient With Pretransplant Papilledema and Persistence After Liver Transplantation (n = 2)

Two patients developed signs of mild papilledema before LT (2/41, 4.9%). For 1 patient, the papilledema was observed at 2 years

TABLE 1. Characteristics of the study population

	Papilledema, n = 9	Nonpapilledema, n = 60	*P*
Age at presentation, y	1 (1;1.25)	1 (1;1)	
Female	7 (78)	52 (86)	0.6
Diagnostic criteria for Alagille syndrome (/5)	4 (4;5)	4 (3;5)	
Heart	8 (89)	56 (93)	0.51
Liver	9 (100)	60 (100)	1
Butterfly vertebrae	7 (78)	31 (52)	0.17
Ophthalmic abnormality	9 (100)	44 (73)	0.1
Face	8 (89)	48 (80)	1
Pathogenic variant			
JAG1	3 (33)	27 (45)	0.72
NOTCH2	0	0	
Unknown	6 (67)	33 (55)	
LT	8 (89)	32 (53)	0.07
Age at LT, mo	42 (32;51)	32 (21;51)	
Follow-up time, mo	64 (44;109)	60 (12,138)	0.42
Immunosuppressive regimen[†]			
Tacrolimus	6	27	0.61
Cyclosporine	2	5	
Ophthalmic evaluation in patients without LT	1	28 (70)	
Embryotoxon	1	16	1
Papilledema	1	0	0.03*
Pseudopapilledema	0	4	1
Hypopigmented retinopathy	0	2	1
Ophthalmic evaluation before LT (transplanted patients)[†]	8 (89)	32 (53)	
Embryotoxon	3	14	1
Papilledema	2	0	0.2
Pseudopapilledema	0	2	1
Hypopigmented retinopathy	0	3	1
Ophthalmic evaluation after LT[†]	8 (89)	32 (53)	
Embryotoxon	5	15	0.69
Papilledema	8	0	0.0001*
Pseudopapilledema	0	6	0.31
Hypopigmented retinopathy	0	5	0.56

The data are presented as the number (percentage) or median (interquartile range), as appropriate.
LT = liver transplantation.
*Statistically significant difference ($P \leq 0.05$).
[†]Calculated for patients who had undergone LT, n = 8 for papilledema group and n = 32 for nonpapilledema group.

follow-up without evolution. Spontaneous resolution was noted at the 3-year follow-up appointment after LT. The other patient showed resolution of papilledema but had a pale optic disc in both eyes at the last visit (10 years follow-up). Both patients had normal findings on neurological examination, and as the papilledema was mild it was decided to not perform further examinations.

Patients With Papilledema Occurring After Liver Transplantation But With Spontaneous Resolution (n = 1)

One patient developed mild papilledema 6 months after LT. According to the previous explained management, no further examinations were performed. At follow-up, 1.5 years after LT, we observed nearly complete resolution of papilledema. The patient further developed PPO that remained stable during the ensuing 3 years of follow-up after LT.

Patient With Papilledema and Signs of Intracranial Hypertension After Liver Transplantation (n = 5)

The characteristics of the 5 remaining cases with a diagnosis of ICHT (5/69, 7.2%) are summarized in Table 2. These patients did not experience major infectious complications or rejection. The evolution of the condition, as determined by fundoscopy, is shown for patients 2 and 3 in Figure 1. Patient 1 was considered to have probable ICHT because the lumbar puncture opening pressure was just under the upper limit (normal = 25 cm H_2O) and was treated accordingly. Case 3 was the first patient in this cohort to present with papilledema and was treated only with a glucocorticoid according to the protocol followed at that time. The evolution of ICHT in case 4 was fulminant, and a ventriculoperitoneal shunt (VPS) was placed early (<3 months after the onset of the symptoms) to avoid loss of vision. Furthermore, this patient required a skull flap because of persistent papilledema and progressive visual loss, despite the VPS and medical treatment. The papilledema improved initially but then worsened. He finally responded when he was switched from tacrolimus to cyclosporine and acetazolamide. Acetazolamide was helpful in 4 patients, 3 of whom are still being treated with this agent. The remaining case (patient 1) was switched to furosemide because of intolerance to acetazolamide.

Ophthalmic Follow-up and Algorithm for Management of Papilledema/Intracranial Hypertension

In Figure 2, we propose an algorithm for follow-up of ophthalmic complications in patients with ALGS and for

TABLE 2. Clinical data for patients with Alagille syndrome and intracranial hypertension

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ALGS description					
Diagnostic criteria (/5)	5	4	5	3	5
Age at ALGS diagnosis, mo	1	2	1	1	1
Pathogenic variant	JAG1	JAG 1	NR	NR	NR
LT history					
LT indication	Severe cholestasis	Refractory pruritus	First: severe cholestasis Second: PTLD on liver graft	Severe cholestasis	Severe cholestasis
Age at LT, mo	16	37	First: 77 Second: 91	21	50
IS drugs	T, GC	T, GC	C, GC	T, GC	T, GC
Papilledema history					
Age at Papilledema diagnosis, mo	35	43	103	55	62
Time after LT, mo	20	6	12	34	12
Symptoms	None	None	Headache	Headache and visual disturbance	None
Neurological examination	Normal	Normal	Normal	Normal	Normal
Fundus abnormality	Bilateral papilledema	Bilateral papilledema	Bilateral papilledema	Bilateral papilledema Retinopathy	Bilateral papilledema
Visual acuity	10/10	4/10	10/10	6/10	10/10
Visual-evoked potentials	Normal	Nd	Normal	Bilateral abnormal prechiasmatic conduction defect	Normal
Cerebral MRI	Normal	Normal	Normal	Nonspecific white matter abnormality	Normal
CSF pressure ($n < 25$ cmH_2O)	23 cmH_2O*	38 cmH_2O	45 cmH_2O	78 cmH_2O	47 cmH_2O
CSF composition	Normal	Normal	Normal	Normal	Normal
Treatment	Acetazolamide then furosemide†	Acetazolamide	Dexamethasone	Acetazolamide + GC	Acetazolamide + GC
Switch T to C	Yes	No	No	Yes	Yes
VPS	No	No	No	Yes	Yes
Outcome	Resolution	Resolution	Resolution	Resolution	Resolution
Last follow-up	June 2018	June 2018	May 1998	June 2018	May 2018

ALSG = Alagille syndrome; C = cyclosporin; CSF = cerebrospinal fluid; GC = glucocorticoid; IS = immunosuppressive; LT = liver transplantation; MRI = magnetic resonance imaging; N = normal; NR = not realized; PTLD = posttransplant lymphoproliferative disorder; T = tacrolimus; VPS = ventriculoperitoneal shunt.

*Considered as probable intracranial hypertension (ICHT) because the lumbar puncture opening pressure was just under the upper limit (12).

†Attributable to acetazolamide allergy.

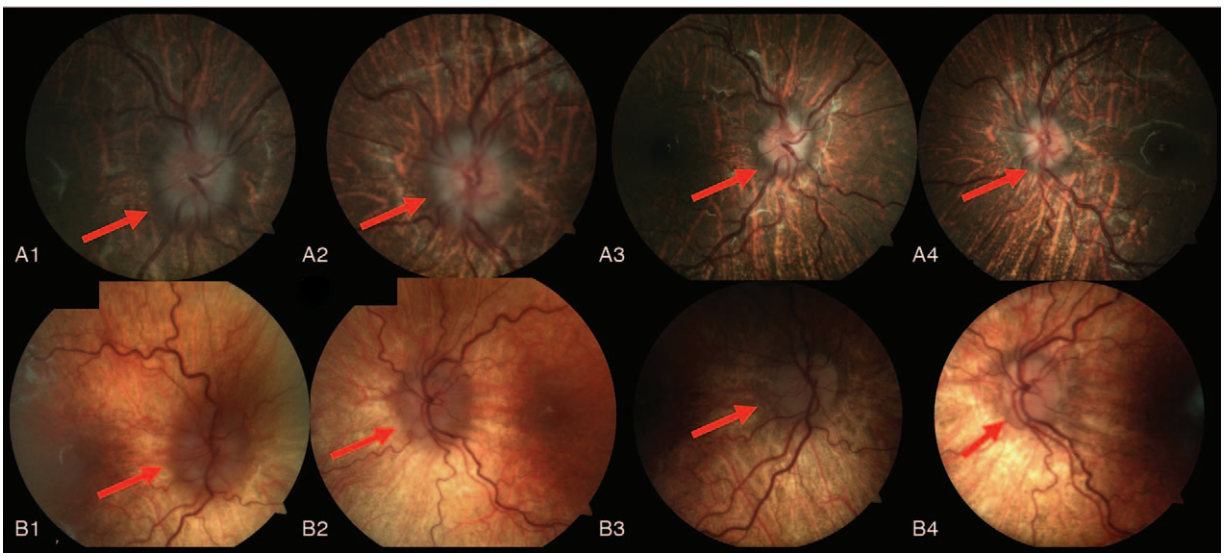

FIGURE 1. Results of fundoscopy in patient 1 (A) and 2 (B). The right eye (A1) and left eye (A2) at diagnosis. The right eye (A3) and left eye (A4), 14 months after treatment. The right eye (B1) and left eye (B2) at diagnosis. The right eye (B3) and left eye (B4), 19 months after treatment. Red arrow: margins of optic nerve, blurred with papilledema (AB1–AB2) and normal with treatment (AB3–AB4).

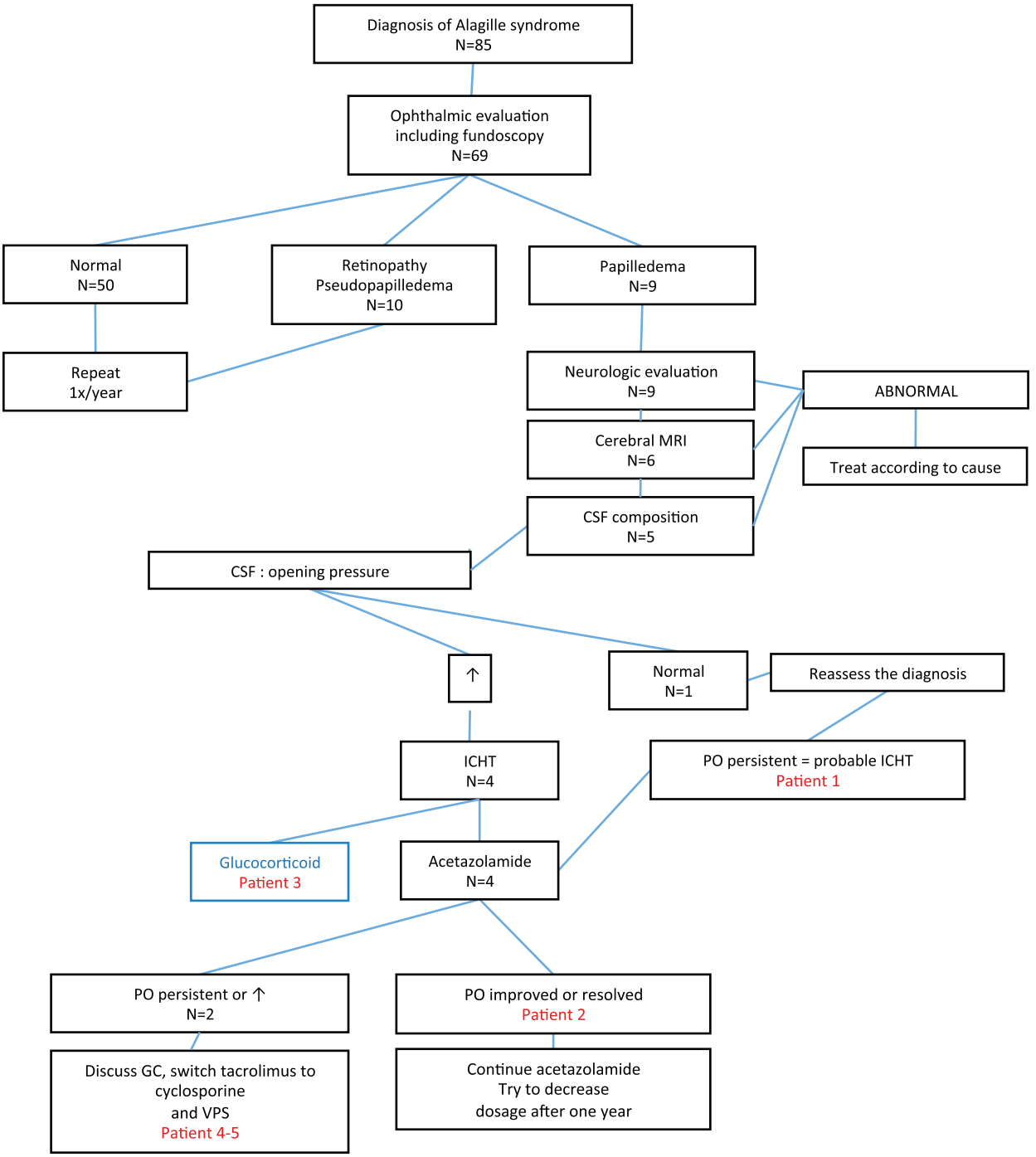

FIGURE 2. Algorithm for ophthalmic follow-up and management of papilledema and intracranial hypertension in patients with Alagille syndrome. The trajectory of the 85 patients is presented. In blue, management of patients that we would not recommend anymore. CSF = cerebrospinal fluid; GC = glucocorticoid; ICHT = intracranial hypertension; N, number; PO = papilledema; VPS = ventriculoperitoneal shunt.

management of suspected papilledema and ICHT. The trajectory of the 85 patients observed was added for more understanding.

Other Ophthalmic Complications

We detected PPO in 10 (14.4%) of the 69 patients, including 4 nontransplant patients. Two patients with pretransplant PPO remained stable during follow-up. In 4 patients, drusen became progressively more visible. The 10 patients remained asymptomatic including stable ophthalmic evaluations with no apparent visual loss, decrease in visual acuity, or abnormal visual evoked potentials. Hypopigmented retinopathy was diagnosed in 7 (10.1%) of the 69 patients and was associated with PPO in 2 nontransplant patients. None of the patients with hypopigmented retinopathy, but without an ODA, experienced a decrease in vision.

TABLE 3. Comparison of patients with and without Alagille syndrome who underwent liver transplantation

	LT for ALGS (n = 40)	LT for other indications (n = 40)	*P*
Indication of transplantation			
ALGS	40 (100)	0	
Biliary atresia	0	28 (70)	
Familial cholestasis	0	4 (10)	
Inborn error of metabolism	0	4 (10)	
Malignancy	0	3 (7,5)	
Cirrhosis	0	1 (2,5)	
Age at transplant, mo	36 (21;51)	11 (8;26)	
Immune suppression			
Tacrolimus	33 (82)	40 (100)	
Cyclosporine	7 (17)	0	
Ophthalmic evaluation before LT			
Embryotoxon	17 (42)	0	0.0001*
Papilledema	1 (2,5)	1 (2,5)	1
Pseudopapilledema	2 (5)	0	0.49
Hypopigmented retinopathy	3 (7,5)	0	0.24
Ophthalmic evaluation after LT			
Embryotoxon	20 (50)	0	0.0001*
Papilledema	8 (20)	1 (2,5)	0.03*
Pseudopapilledema	6 (15)	0	0.05*
Hypopigmented retinopathy	5 (12)	0	0.05*

The data are presented as the number (percentage) or median (interquartile range), as appropriate.
ALGS = Alagille syndrome; LT = liver transplantation.
*Statistically significant difference ($P \leq 0.05$).

Comparison Between Alagille Syndrome and the Non-Alagille Cohort After Liver Transplantation

Forty of the 69 patients with ALGS were transplanted. They are compared in Table 3 with the non-ALGS cohort transplanted for other indication. There was a significant association of presence of embryotoxon and PPO and retinopathy with ALGS before and after LT. Only 1 (2.5%) of the 40 patients in the non-ALGS cohort developed papilledema. This patient developed papilledema after LT and was switched from tacrolimus to cyclosporine, but it is unclear whether the improvement was spontaneous or the result of the drug switch.

DISCUSSION

This case series of 9 patients with ALGS and papilledema, including 5 with confirmed or probable ICHT, is the largest published series to date. PPO with drusen of the optic nerve is a commonly reported ophthalmic abnormality in patients with ALGS with an incidence of approximately 65% (4,8–10,26). Some cases of papilledema without ICHT have been mentioned in earlier series but not described and only 6 cases of ICHT have been described in patients with Alagille syndrome in the literature (8,14). Narula et al first described this complication in 4 patients with ALGS, who developed ICHT in the context of PPO. Three of these patients had undergone LT and were treated with cyclosporine or tacrolimus (8). Mouzaki et al (14) described 2 patients with ALGS who had not undergone LT but developed ICHT with papilledema before the age of 3 years. The incidence rates of 13% for papilledema and 7% for ICHT in our cohort suggest that these complications should be considered as part of ALGS. It is possible that papilledema and ICHT develop with age in these patients and this is suggested by the median follow-up period of 60 months.

Cerebrovascular abnormalities, including moyamoya disease, are increasingly described in patients with ALGS (27–29) and are generally attributed to abnormalities in the *NOTCH* signaling pathway. *JAGGED* interacts with *NOTCH* signaling during differentiation of smooth muscle cell and in angiogenic vascular remodeling (27–30). Moreover, *NOTCH* pathway genes have been reported to be important in the development of the eye in mice (31). It is possible that the *NOTCH* pathway has an effect on the vascularization and development of the eye. Alternatively, alterations in *JAG1* may have an effect on the development of papilledema and ICHT as a result of abnormal production of CSF or its resorption in the choroid plexus (8,14,32–34). Progression of these complications may be age related.

This case series underscores the importance of close follow-up for ophthalmic complications in patients with ALGS (8,14). In Figure 2, we proposed an algorithm for ophthalmic follow-up and management of papilledema and intracranial hypertension. Our patients underwent yearly ophthalmic follow-up and we observed newly ophthalmic complications within the time. For this reason, we would recommend an annual ophthalmic testing.

In our cohort, we identified 5 patients with ICHT who were at risk of vision loss in the absence of or despite of treatment. Two of the 5 patients showed a decrease in visual acuity, which was particularly marked in patient 4. The remaining 3 patients had no symptoms and were diagnosed during a routine check-up. Three patients who had undergone LT had spontaneous resolution of papilledema that could have been missed without routine ophthalmic evaluation.

No further work-up, including measurements of lumbar pressure or magnetic resonance imaging, was undertaken in patients with only mild signs of papilledema. They were, however, followed at least once a year. The diagnostic criteria for idiopathic ICHT in children were revised in 2013 (12) such that lumbar pressure measurements and findings on cerebral imaging form part of the diagnostic criteria for ICHT in children. In line with these recommendations, we would advocate the use of these examinations in

any ALGS patient who has persistent, asymptomatic, symptomatic, or true severe papilledema (7).

Ophthalmic complications in relation with papilledema seem to appear mostly after LT, which raises the question of whether or not progressive development of ophthalmic complications is attributable to LT/immunosuppression or follow-up bias. Our study contained a degree of bias in that the number of patients and duration of follow-up were greater in the transplanted cohort. It is also possible that there is an association between tacrolimus and development of papilledema as this occurred after onset of tacrolimus therapy and improved after switching from tacrolimus to cyclosporine. There is a previous case of neurotoxicity suspected to be attributable to tacrolimus (35,36). ICHT has been described as part of posterior reversible encephalopathy syndrome, which is associated with tacrolimus toxicity (37). The mechanism underlying this syndrome is thought to involve vasogenic edema of the brain caused by abnormal vascular tone and permeability (38,39). In our patients, the same mechanisms may be responsible for papilledema and ICHT, even in the absence of clinical signs of posterior reversible encephalopathy syndrome (39).

The treatment and response to treatment varied from patient to patient. Acetazolamide is generally the first-line treatment and is administered at a dose of 25 to 100 mg/kg/day. The response to this agent was good in 3 of 4 patients. Acetazolamide decreases CSF production by inhibiting of carbonic anhydrase (40). Furosemide is widely considered as the second-line therapy in patients with allergy or no response to acetazolamide. Currently, glucocorticoids are less frequently prescribed as first-line treatment for ICHT because of their side effects but could be added in severe cases where vision is threatened. If ICHT develops, it may be necessary to consider a switch from tacrolimus to cyclosporine, which was associated to a favorable outcome in 3 of our patients. If the papilledema relapses or worsens, placement of a VPS should be considered.

This study has some limitations. The first limitation is the retrospective design. Sixteen patients were excluded because of missing ophthalmic follow-up data. It is likely that some patients may have had asymptomatic papilledema or PPO, which could have decreased the calculated incidence. Furthermore, both participating institutions are tertiary centers that mainly treat severely affected patients with indications for LT, which may have introduced a degree of selection bias. The inclusion criteria included at least 1 ophthalmic control and we could not explore the long-term natural history of these ophthalmic complications. Despite these limitations, this is the largest study to date to describe papilledema and ICHT as part of ALGS, especially in ALGS who have undergone LT.

In accordance with the findings of this study, we suggest that papilledema and ICHT should be considered as part of the ALGS. All patients with ALGS should have regular ophthalmic follow-up. This is particularly true in patients who have undergone LT, because of the high risk of loss of vision associated with papilledema and ICHT. When papilledema is detected, a complete neurologic work-up, including cerebral magnetic resonance imaging and measurement of the lumbar opening pressure should be performed, and treatment with acetazolamide must be implemented immediately. A switch from tacrolimus to another calcineurin inhibitor and placement of a VPS should be considered in refractory cases.

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REFERENCES

1. Alagille D, Odièvre M, Gautier M, et al. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *J Pediatr* 1975;86:63–71.
2. Krantz ID, Piccoli DA, Spinner NB. Clinical and molecular genetics of Alagille syndrome. *Curr Opin Pediatr* 1999;11:558–64.
3. Subramaniam P, Knisely A, Portmann B, et al. Diagnosis of Alagille syndrome-25 years of experience at King's College Hospital. *J Pediatr Gastroenterol Nutr* 2011;52:84–9.
4. Kamath BM, Schwarz KB, Hadzić N. Alagille syndrome and liver transplantation. *J Pediatr Gastroenterol Nutr* 2010;50:11–5.
5. Kamath BM, Loomes KM, Piccoli DA. Medical management of Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2010;50:580–6.
6. Ovaert C, Germeau C, Barrea C, et al. Elevated right ventricular pressures are not a contraindication to liver transplantation in Alagille syndrome. *Transplantation* 2001;72:345–7.
7. MacBride EK. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *J Pediatr Gastroenterol Nutr* 2002;35:103–4.
8. Narula P, Gifford J, Steggall MA, et al. Visual loss and idiopathic intracranial hypertension in children with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2006;43:348–52.
9. Hingorani M, Nischal KK, Davies A, et al. Ocular abnormalities in Alagille syndrome. *Ophthalmology* 1999;106:330–7.
10. El-Koofy NM, El-Mahdy R, Fahmy ME, et al. Alagille syndrome: clinical and ocular pathognomonic features. *Eur J Ophthalmol* 2011;21:199–206.
11. Hamann S, Malmqvist L, Costello F. Optic disc drusen: understanding an old problem from a new perspective. *Acta Ophthalmol* 2018;96:673–84.
12. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013;81:1159–65.
13. Schirmer CM, Hedges TR. Mechanisms of visual loss in papilledema. *Neurosurg Focus* 2007;23:E5.
14. Mouzaki M, Nichter C, Qureshi M, et al. Idiopathic intracranial hypertension in two patients with Alagille syndrome. *J Child Neurol* 2010;25:1006–8.
15. Kamath BM, Bauer RC, Loomes KM, et al. NOTCH2 mutations in Alagille syndrome. *J Med Genet* 2012;49:138–44.
16. McDaniell R, Warthen DM, Sanchez-Lara PA, et al. NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet* 2006;79:169–73.
17. Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. *Nat Genet* 1997;16:235–42.
18. Kamath BM, Baker A, Houwen R, et al. Systematic review: the epidemiology natural history, and burden of Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2018;67:148–56.
19. Muñoz-Aguilar G, Domingo-Triadó I, Maravall-Llagaria M, et al. Previously undescribed family mutation in the JAG1 gene as a cause for Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2017;64:e135–6.
20. Van den Berg M, Rings E, Stokkers P. Genetic basis of Alagille syndrome deciphered. *J Pediatr Gastroenterol Nutr* 1998;27:370–1.
21. Rand EB. The genetic basis of the Alagille syndrome. *J Pediatr Gastroenterol Nutr* 1998;26:234–6.
22. Batthi and al. The Patient With Decreased Vision: Classification and Management. Optic Disc Drusen. In Basic and Clinical Science Course. Neuro-Ophthalmology. American Academy of Ophthalmology. 2007–2008;129.
23. Varma S, Stéphenne X, Komuta M, et al. The histological quantification of alpha-smooth muscle actin predicts future graft fibrosis in pediatric liver transplant recipients. *Pediatr Transplant* 2017;21:.
24. Varma S, Ambroise J, Komuta M, et al. Progressive fibrosis is driven by genetic predisposition, allo-immunity, and inflammation in pediatric liver transplant recipients. *EBioMedicine* 2016;9:346–55.
25. Demaret T, Varma S, Vainilovich Y, et al. Liver transplantation does not impact the renal function outcome in Alagille syndrome. [Abstract] In: Abstract book of the 50th ESPGHAN annual meeting; 2017 10–13 May, Prague, Czech Republic. Abstract H-P-602.
26. Nischal KK, Hingorani M, Bentley CR, et al. Ocular ultrasound in Alagille syndrome: a new sign. *Ophthalmology* 1997;104:79–85.
27. Carpenter CD, Linscott LL, Leach JL, et al. Spectrum of cerebral arterial and venous abnormalities in Alagille syndrome. *Pediatr Radiol* 2018;48:602–8.
28. Emerick KM, Krantz ID, Kamath BM, et al. Intracranial vascular abnormalities in patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2005;41:99–107.

29. Kamath BM, Spinner NB, Emerick KM, et al. Vascular anomalies in Alagille syndrome: a significant cause of morbidity and mortality. *Circulation* 2004;109:1354–8.
30. Doi H, Iso T, Sato H, et al. Jagged1-selective notch signaling induces smooth muscle differentiation via a RBP-Jkappa-dependent pathway. *J Biol Chem* 2006;281:28555–64.
31. Bao ZZ, Cepko CL. The expression and function of Notch pathway genes in the developing rat eye. *J Neurosci* 1997;17: 1425–34.
32. Hayreh SS. Pathogenesis of optic disc edema in raised intracranial pressure. *Prog Retin Eye Res* 2016;50:108–44.
33. Ben J, Kim, Anne B, et al. The genetics and ocular findings of Alagille syndrome. *Semin Ophthalmol* 2007;22:205–10.
34. Crosnier C, Attie-Bitach T, Encha-Razavi F, et al. JAGGED1 gene expression during human embryogenesis elucidates the wide phenotypic spectrum of Alagille syndrome. *Hepatology* 2000;32: 574–81.
35. Emre S, Genyk Y, Schluger LK, et al. Treatment of tacrolimus-related adverse effects by conversion to cyclosporine in liver transplant recipients. *Transpl Int* 2000;13:73–8.
36. Cilio MR, Danhaive O, Gadisseux JF, et al. Unusual cyclosporin related neurological complications in recipients of liver transplants. *Arch Dis Child* 1993;68:405–7.
37. Wolff V, Jeung MY, Kessler R, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. *Eur Neurol* 2010;64:169–77.
38. Wu Q, Marescaux C, Wolff V, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. *Eur Neurol* 2010;64:169–77.
39. Facchini A, Magnoni S, Civelli V, et al. Refractory intracranial hypertension in posterior reversible encephalopathy syndrome. *Neurocrit Care* 2013;19:376–80.
40. Aylward SC, Reem RE. Pediatric intracranial hypertension. *Pediatr Neurol* 2017;66:32–43.