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ORIGINAL ARTICLE

Severe Dengue and Associated Hemophagocytic Lymphohistiocytosis in PICU

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Abstract

Objectives To study the clinico-laboratory profile and outcome of children with severe dengue and dengue-associated hemophagocytic lymphohistiocytosis (HLH).

Methods In this retrospective study, 22 children with laboratory confirmed severe dengue admitted to pediatric intensive care unit (PICU) were enrolled. Clinical features, laboratory parameters, and outcome were noted and compared between cases fulfilling HLH-2004 criteria and those without HLH.

Results Median (IQR) age was 8 (5–10.3) y. Fever was present for mean (SD) duration of 5.3 (2.1) d. Vomiting, respiratory distress, pain abdomen and hepatomegaly were other clinical features. Thrombocytopenia, anemia and elevated serum transaminases were noted in 91%, 41% and 30% respectively; coagulopathy and hypoalbuminemia were seen in 36% each. Half ($n = 11$, 50%) had dengue shock syndrome. Acute respiratory distress syndrome (ARDS) ($n = 7$, 32%) and acute kidney injury (AKI) ($n = 6$, 28%) were other major organ dysfunctions. Mean (SD) duration of PICU stay was 3.6 (1.5) d with 13.6% mortality. HLH was noted in 7 (32%) cases at a median (IQR) hospital stay of 5 (2–8) d. Children with HLH had significantly higher Pediatric Index of Mortality 2 (PIM 2) score at admission and higher frequency of pain abdomen, anemia, hypoalbuminemia, elevated alanine aminotransferase (ALT) and ARDS. Length of PICU stay (5.1 *vs*. 2.9 d) and mortality (28.6% *vs*. 6.7%) were higher in HLH group, however the difference was not statistically significant. Steroids were used in 4 cases with HLH and all survived, whereas among 3 who did not receive steroids, 2 died ($p = 0.23$).

Conclusions Severe dengue presents with life-threatening organ dysfunctions. HLH is increasingly recognized in dengue infection and maybe considered as a differential diagnosis in children with lower hemoglobin, hypoalbuminemia, elevated ALT and severe organ dysfunction.

Keywords Dengue · Hemophagocytic lymphohistiocytosis · Children · PICU · India

Introduction

Dengue fever is a mosquito-borne viral infectious disease contributing significantly to morbidity and mortality in south east Asian endemic regions. The pathogenesis of severe disease such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) is attributed to antibody dependent enhancement, massive T cell activation, cytokine storm, capillary leak, and coagulopathy [1]. Severe dengue is associated with various complications such as encephalopathy, liver dysfunction, myocardial dysfunction, and acute renal failure.

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon but potentially life-threatening complication of dengue infection. HLH is characterized by unregulated proliferation of activated lymphocytes and Natural Killer (NK) cells, uncontrolled production of pro-inflammatory cytokines (IL-6, IL-10, IL-35, CCL3, GM-CSF, IFN-γ and TNF-α) (hyperinflammation/cytokine storm), inappropriate macrophage stimulation in bone marrow and phagocytosis of blood cells, especially erythroid lineage leading to multiple organ dysfunction syndrome (MODS) [2, 3].

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The clinical manifestations include prolonged fever, pancytopenia, jaundice, liver dysfunction, hepatosplenomegaly, organ dysfunction, and death [4, 5]. Its diagnosis is still largely based on the clinical and laboratory criteria of HLH 2004 guidelines though several modifications have been proposed since its publication [6]. In infection associated HLH, timely recognition of the syndrome and aggressive treatment to control the trigger of HLH with or without HLH-specific immunotherapy are important in decreasing the mortality. In dengue-endemic countries, HLH syndrome is likely to be under-diagnosed due to overlapping clinical features with dengue (fever, hepatosplenomegaly, leukopenia, and thrombocytopenia) [7, 8]. Persistence of fever beyond 7 d, elevated transaminases, progressive cytopenia and organ dysfunction may alert clinicians to suspect underlying HLH [9, 10]. The delayed diagnosis or non-diagnosis of dengue associated HLH can have therapeutic implications and may affect the outcome.

Recent literature on HLH in dengue is emerging from endemic regions in both adults and children [9–17]. The present study was conducted in a cohort of children admitted to intensive care during 2017 outbreak season to study the clinico-laboratory profile and outcome of severe dengue and associated HLH.

Material and Methods

This is a retrospective study conducted in a 15-bed Pediatric intensive care unit (PICU) of a tertiary care teaching hospital in North India. All children admitted with severe dengue during 2017 post monsoon outbreak season (July to November) were enrolled. Dengue was diagnosed if children with suggestive clinical features tested positive for NS1 antigen or IgM antibodies in a single serum by ELISA method. Severe dengue was defined as per World Health Organization guidelines [18]. Children with co-infections were excluded. Approval from Institute Ethics Committee was sought.

The data was collected on predesigned proforma from electronic database of the unit as well as admission records. Informed consent was waived as the study involved collection of existing data. Demographic and clinical features and laboratory parameters at admission, including hemoglobin, platelet count, white blood cell count, serum albumin, coagulation profile, liver function tests and renal function tests were recorded. The Pediatric Index of Mortality (PIM)-2 score was noted as a measure of illness severity. Various complications including cytopenia, coagulopathy (INR >1.5), liver dysfunction, acute kidney injury (AKI – defined as per KDIGO guidelines [19]), shock, and acute respiratory distress syndrome (ARDS) and organ supportive therapies such as mechanical ventilation, need for vasoactive drugs and renal replacement therapy (RRT) were noted. The outcome included length of PICU stay and mortality.

Hemophagocytic lymphohistiocytosis (HLH) was suspected clinically in children with severe dengue who had one or more of the following; persistence of fever, progressive cytopenia and worsening organ dysfunction despite supportive care. Diagnosis was made using HLH-2004 criteria [6]. The decision to treat HLH with steroids was taken by treating physicians on case-to-case basis guided by the severity of organ dysfunction and clinical course. Cases with HLH were compared with those not having HLH with regard to clinical and laboratory parameters, various complications, interventions, and outcome.

Data entry was done in Microsoft excel 2013 (Microsoft, Redmond, WA, USA) and statistical analysis was performed on SPSS software version 21 (IBM Crop. 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA). Baseline categorical variables were summarized as frequency (percentage) and continuous variables were summarized in mean (SD) or median (IQR). Comparative analysis was carried out using Chi-Square or Fisher's exact test for categorical variables and Student-t test for continuous variables. The p value <0.05 was considered significant.

Results

During the 2017 outbreak season, 22 cases with severe dengue were admitted to PICU. The median (IQR) age was 8 (5–10.3) y and 15 (68.2%) were males. Fever was present for a mean (SD) duration of 5.3 (2.1) d. Other common clinical features were hepatomegaly (72.7%), vomiting (68.2%), respiratory distress (59%), pain abdomen (50%), encephalopathy (36.4%), seizures (27.2%), bleeding (18.2%), and splenomegaly (9.1%). Anemia (Hb <10 g%), leucopenia (WBC <4000/cumm), and thrombocytopenia (platelet count <100000/cumm) were noted in 41%, 13.6%, and 91% cases, respectively. Other complications noted were coagulopathy (36.4%), hypoalbuminemia (36.4%), AKI (27.3%), ARDS (32%), and shock (50%). Mechanical ventilation and vasoactive drugs were needed in 6 (27.3%) cases each, and 2 (9%) underwent renal replacement therapy (RRT). The mean (SD) length of PICU stay was 3.6 (1.5) d and mortality was 13.6% ($n = 3$) (Table 1).

Seven out of 22 cases (32%) were diagnosed with HLH at a median (IQR) stay of 5 (2–8) d (Table 2). On comparison, children with HLH had significantly higher PIM2 score at admission. They had higher frequency of pain abdomen, significantly lower hemoglobin and serum albumin, elevated ALT and higher incidence of ARDS (Table 3).

In the HLH group, out of 7 children, 4 were treated with intravenous methylprednisolone (30 mg/kg, maximum dose

Table 1 Clinical and laboratory profile of children with severe dengue admitted to PICU

Characteristics	Total cases, $n = 22$
Age (in years), median (IQR)	8 (5–10.3)
Male, n (%)	15 (68.2)
Fever, n (%)	22 (100)
Duration of fever (in days), mean (SD)	5.3 (2.1)
Clinical features	
Hepatomegaly, n (%)	16 (72.7)
Vomiting, n (%)	15 (68.2)
Respiratory distress, n (%)	13 (59.1)
Pain abdomen, n (%)	11 (50)
Shock, n (%)	11 (50)
Encephalopathy, n (%)	8 (36.4)
Seizure, n (%)	6 (27.2)
Bleeding, n (%)	4 (18.2)
Splenomegaly, n (%)	2 (9.1)
PIM2 score, mean (SD)	9.42 (2.9)
Laboratory features	
Anemia (Hb < 10 g/dl), n (%)	9 (40.9)
Hemoglobin (g%), mean (SD)	10.9 (2.1)
Leucopenia (WBC count <4000 per cumm), n (%)	3 (13.6)
WBC count (per cumm), mean (SD)	7232 (2421)
Platelet count <100000 per cumm, n (%)	20 (90.9)
Platelet count (per cumm), mean (SD)	48014 (8464)
Coagulopathy, n (%) (INR >1.5)	8 (36.4)
Aspartate transaminase (AST) >1000 IU/L, n (%)	6 (27.3)
AST (IU/L), mean (SD)	1595 (839)
Alanine transaminase (ALT) >1000 IU/L, n (%)	6 (27.3)
ALT (IU/L), mean (SD)	1405 (666)
Hypoalbuminemia (Albumin <2.5 g%), n (%)	8 (36.4)
Albumin (g%), mean (SD)	2.5 (0.5)
Complications and outcome	
HLH, n (%)	7 (31.8)
Acute kidney injury, n (%)	6 (27.3)
ARDS, n (%)	7 (31.8)
Invasive mechanical ventilation, n (%)	6 (27.3)
Shock, n (%)	11 (50)
Received vasoactive drugs, n (%)	6 (27.3)
Length of PICU stay (in days), mean (SD)	3.6 (1.5)
Mortality, n (%)	3 (13.6)

ARDS Acute respiratory distress syndrome; *HLH* Hemophagocytic lymphohistiocytosis; *PICU* Pediatric intensive care unit; *WBC* White blood cells

1 g, once daily for 5 d) followed by oral prednisolone weaning over next 2 wk. All children who received steroids survived whereas among those who did not receive steroids, 2 died ($p = 0.143$). The length of PICU stay (5.1 vs. 2.9 d) and mortality (28.6% vs. 6.7%) were higher in HLH group, however the difference was not statistically significant.

Discussion

It was noted that out of 22 children with severe dengue, seven (32%) were complicated by HLH. Children with HLH had significantly higher frequency of pain abdomen, anemia, severe hypoalbuminemia, elevated ALT and ARDS. HLH is a relatively recently recognized but life-threatening complication of dengue infection, categorized under expanded dengue syndrome in the revised classification [18].

The diagnosis of infection associated HLH is often challenging, particularly in dengue, as many clinical and laboratory criteria overlap with features of severe infection. Pal et al. reported 8 children with dengue-associated HLH and noted that fever, capillary leak, thrombocytopenia, hyperferritinemia, coagulopathy, and elevated transaminase levels were common features. All children were treated with dexamethasone, one received IVIG as a rescue measure, along with supportive care [9]. In another report from south India, 23 out of 212 children with dengue had associated HLH. They presented with lower hemoglobin, falling platelet counts, elevated erythrocyte sedimentation rate and coagulopathy. Nineteen children received IVIG and all survived, whereas 4 did not receive IVIG, of which 3 died [14]. A study from Puerto Rico showed that cases with HLH were younger (median age: 1 *vs*. 13 y, $p < 0.01$), had longer hospital stay (18 *vs*. 5 d, $p < 0.01$), required PICU admission (100% *vs*. 16%, $p < 0.01$); and higher proportion of them had hepatomegaly, splenomegaly, lymphadenopathy, anemia, and elevated liver transaminases [16].

A recent systematic review and meta-analysis of 122 cases of dengue-associated HLH in both adults and children from South-East Asia, Western Pacific region, and America found fever (97.2%), thrombocytopenia (90.1%), splenomegaly (78.4%), anemia (76.0%), hepatomegaly (70.2%) and serum ferritin ≥500 μg/L (97.1%) as common features. The authors suggested long duration of fever, persistent low platelet count, high serum ferritin, and elevated lactate dehydrogenase levels could serve as indicators for underlying dengue-associated HLH [20].

In the present cohort, fever, thrombocytopenia, hypofibrinogenemia, hyperferritinemia and hemophagocytosis in bone marrow were seen in all children with HLH, while anemia was seen in 86%, hypertriglyceridemia in 29% and splenomegaly in 14%. Children with HLH were noted to have higher incidence of complications, particularly ARDS and AKI. Some of the clinical and laboratory variables could help in recognizing associated HLH earlier. Anemia, in particular, can be a specific distinguishing marker as severe dengue with plasma leakage is classically associated with hemoconcentration unless the course is complicated by significant hemorrhage. Hence, a lower hemoglobin without clinical

Table 2 Different HLH parameters and their progression in children with dengue-associated HLH ($n = 7$)

HLH 2004 criteria	N (%)	Day of PICU stay		
		Day 1	Day 3	Day 5
Presence of fever, n (%)	7 (100)	7 (100)	4 (57)	3 (43)
Splenomegaly, n (%)	1 (14.3)			
Hemoglobin <10 g/dl	6 (85.7)			
Hemoglobin, Mean (SD) g/dl		8.1 (2.8)	8.7 (3.0)	7.4 (2.6)
Platelet <100,000/cu mm, n (%)	7 (100)			
Platelet count, Median (IQR)		23000 (18000–36000)	33000 (19000–51000)	46000 (35500–61500)
Absolute neutrophil count <1000/cu mm	0			
Triglyceride >265 mg/dl	2 (28.6)			
Triglyceride, Median (IQR) mg/dl			120 (105–294)	
Fibrinogen <1.5 g/dl	7 (100)			
Fibrinogen, Median (IQR) g/dl			0.94 (0.54–1.42)	
Ferritin >500 μg/L	7 (100)			
Ferritin, (IQR) μg/L			14600 (6424–27368)	
Hemophagocytosis in bone marrow	7 (100)			

or occult bleeding and progressive organ dysfunction should raise a suspicion of underlying HLH. A significantly lower albumin and elevated ALT were also noted in children with HLH, serving as potential markers to identify this complication early.

The treatment of dengue associated HLH is supportive and use of steroids and IVIG have been reported in small studies [13–15]. In the present cohort, children with HLH who received steroids ($n = 4$) in addition to supportive care had favourable outcome as compared to those who received

Table 3 Comparison of clinical and laboratory parameters and complications in children with severe dengue with and without HLH

Characteristics	HLH group ($n = 7$)	No HLH group ($n = 15$)	p value
Age (in years), median (IQR)	8 (3–9)	8 (6–11)	0.59
Male, n (%)	5 (71.4)	10 (66.7)	0.83
Duration of fever (days), mean (SD)	5.14 (1.2)	5.43 (2.4)	0.78
Clinical features			
Respiratory distress, n (%)	4 (57.1)	9 (60)	0.90
Pain abdomen, n (%)	6 (85.7)	5 (33.3)	**0.02**
Shock, n (%)	5 (71.4)	6 (40.0)	0.36
Encephalopathy, n (%)	4 (57.1)	4 (26.7)	0.22
Bleeding, n (%)	1 (14.3)	4 (26.7)	0.93
PIM2 score	13.7 (1.4)	7.4 (2.8)	**0.001**
Hemoglobin (g/dl), mean (SD)	8.1 (2.8)	12.2 (2.3)	**0.0002**
WBC count (per cu mm), mean (SD)	7909 (3766)	6916 (3338)	0.24
Platelet count (per cu mm), median (IQR)	23000 (18000-36000)	44000 (19000-60000)	0.16
INR, mean (SD)	1.96 (0.83)	1.40 (0.53)	0.12
AST (IU/L), median (IQR)	1110 (316–8880)	376 (113–593)	0.10
ALT (IU/L), median (IQR)	940 (548–3241)	237 (120–1311)	**0.02**
Albumin (g/dl), mean (SD)	1.8 (0.8)	2.7 (0.5)	**0.007**
AKI, n (%)	4 (57.1)	2 (13.3)	0.05
ARDS, n (%)	6 (85.7)	1 (6.7)	**0.0006**
Length of PICU stay (days), mean (SD)	5.1 (2.8)	2.9 (1.2)	0.05
Mortality, n (%)	2 (28.6)	1 (6.7)	0.23

AKI Acute kidney injury; *ALT* Alanine transaminase; *ARDS* Acute respiratory distress syndrome; *AST* Aspartate transaminase; *HLH* Hemophagocytic lymphohistiocytosis; *INR* International normalized ratio; *PICU* Pediatric intensive care unit; *WBC* White blood cells

supportive care alone, however the sample size is small to make a meaningful conclusion.

Conclusions

HLH is not uncommon in children with severe dengue admitted to intensive care. Presence of pain abdomen, unexplained anemia, lower albumin and elevated ALT may help to suspect underlying HLH early. Supportive care is the mainstay of treatment and further studies are needed to explore the role of steroids.

Authors' Contribution KN, SKA and MJ conceived the idea. DB and RI collected the data and wrote the first draft. DB and KN performed the statistical analysis. KN and SKA reviewed and revised the manuscript. provided critical inputs and all authors approved the final manuscript. MJ is the guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

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ELECTROPHYSIOLOGY

Left cardiac sympathetic denervation in children with Jervell Lange-Nielsen syndrome and drug refractory torsades – A case series

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Abstract

Introduction: Long QT syndrome is an inherited malignant channelopathy which leads to life-threatening arrhythmia, with multiple genotypes. Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive subtype of this disease, characterized by congenital sensorineural deafness and a high incidence of sudden cardiac death (SCD).

Methodology: We prospectively followed up six children who underwent left cardiac sympathetic denervation (LCSD) for JLNS in view of high-risk features despite being on maximally tolerated doses of oral propranolol.

Results: Mean age at diagnosis was 2.75 ± 0.39 years, with a significant delay between onset of symptoms and diagnosis (mean 7.2 ± 3.5 months). All had sensorineural hearing loss, conforming to the JLNS phenotype. Mean QTc interval was 603 ± 93 ms, with T wave alternans (TWA) seen in all cases. All were started on propranolol and subsequently subjected to LCSD, and 3 underwent AAI permanent pacemaker implantation. Over a mean follow-up of 20 months, there was a significant reduction in QTc (603 ± 93 ms to 501 ± 33 ms, $p = .04$), which was persistent on follow-up (525 ± 41 ms) and only two out of six had persistent T wave alternans on ECG ($p < .01$). None of these children had presyncope, syncope, seizures, torsades de pointes, cardiac arrest or death on follow up following LCSD.

Conclusion: Jervell Lange-Nielsen syndrome is a subtype of LQTS with high-risk features. LCSD, an effective therapeutic option for those having symptoms despite being on propranolol, results in significant reduction of QTc interval and amelioration of symptoms.

KEYWORDS
left cardiac sympathetic denervation, long QT syndrome, propranolol

Abbreviations: JLNS, Jervell Lange Nielsen Syndrome; LCSD, left cardiac sympathetic denervation; LQTS, long QT syndrome; SCD, sudden cardiac death; TWA, T-wave alternans.

TABLE 1 Characteristics of patients with follow-up with JLN syndrome.

Serial No	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at symptom onset (months)	24	33	22	23	9	12
Age at diagnosis (months)	28	38	36	30	13	24
Age at surgery (months)	30	39	37	32	112	25
Sex	Female	Male	Male	Male	Male	Male
Pre-op QTc (ms)	670	770	520	540	550	640
Post-op QTc (ms)	480	460	480	516	550	520
Follow-up QTc (ms)	480	580	520	480	550	540
High risk features	Aborted SCD TWA	Family H/O SCD, TWA	Syncope TWA	Syncope Aborted SCD TWA	Syncope TWA	Syncope TWA
Intervention	LCSD PPI-AAI	LCSD	LCSD PPI-AAI	LCSD	LCSD	LCSD PPI-AAI
Follow-up duration (months)	36	30	25	19	4	33

Abbreviations: LCSD, left cardiac sympathetic denervation; PPI, permanent pacemaker implantation; SCD, sudden cardiac death, TWA, T wave alternans.

1 | INTRODUCTION

Long QT syndrome (LQTS) is an uncommon autosomally inherited cardiac channelopathy which predisposes to malignant arrhythmia. Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive subtype of this disease, characterised by congenital sensorineural deafness and a high incidence of sudden cardiac death (SCD).[1] More than 90% of cases have KCNQ1 mutation, while KCNE1 is involved in rest of the cases. Mortality is high and less than half survive till the second decade.[2]

We report six cases of JLNS with sensorineural hearing loss who underwent left cardiac sympathetic denervation (LCSD) through posterolateral thoracotomy, in view of high-risk features, despite being on maximally tolerated doses of oral propranolol.

2 | METHODOLOGY

The cases were enrolled as a part of a prospective multicentric registry funded by Indian Council of Medical Research. However, all six cases were evaluated and managed in a single tertiary care centre in South India. Children with long QT syndrome, diagnosed using modified Schwartz criteria,[3] and congenital sensorineural deafness, fulfilling the phenotype of JLNS were included. Six children were included who despite being on maximally tolerated propranolol, required LCSD for control of symptoms (Table 1).

As per the institute protocol, all patients are started on oral propranolol which is titrated based on blood pressure and heart rate. LCSD is considered if the proband has persistent T-wave alternans (TWA) despite maximally tolerated therapy. The surgery is performed through posterolateral thoracotomy with resection of stellate ganglion and left sided T1-4 ganglion.

3 | RESULTS

3.1 | Case 1

A 2-year-old girl, second born to a non-consanguineous couple at term, was diagnosed to have bradycardia in the immediate postnatal period. Electrocardiogram showed prolonged QTc interval (670 ms), for which she was started on oral propranolol, and kept on medical follow-up. There was no history of syncope or SCD in the family, but she had significant impairment of hearing and speech. She was detected to have a large patent ductus arteriosus with >2:1 left to right shunting, at 24 months of age which was planned for closure.

At the time of PDA device closure, she developed polymorphic ventricular tachycardia which was cardioverted with DC shock, and she was referred to our institute for further evaluation and management. Family screening with ECG showed normal QTc in all members, and a 24-h Holter monitoring showed persistent T wave alternans, despite beta blocker therapy. Hence, she underwent surgical interruption of ductus, along with LCSD and epicardial permanent pacemaker implantation. Oral propranolol was continued, and she has been followed up for 36 months, with no cardiac adverse events.

3.2 | Case 2

A 3-year-old boy with sensorineural hearing loss and impaired speech was planned for cochlear implantation. However, during pre-operative evaluation, he was found to have prolonged QTc (770 ms) with persistent TWA. There was history of deafness in the elder sibling, who had SCD. Screening of other family members were negative.

He was started on oral propranolol, on which there was a reduction of QTc (480 ms) with the resolution of T wave alternans. He underwent

TABLE 2 Comparison of index study to previously published studies.

Author (Year)	Sample size	Age at procedure	Procedure	Outcome
Silver et al.[11]	1	33 months	LCSD + ICD placement	At 30 months of age, he has had occasional episodes of TdP with 42 total appropriate and successful ICD shocks
Collura et al.[14]	18	Mean age 9.7 ± 8.9 years	LCSD + ICD in 10, LCSD in 8	At follow-up of 16.6 ± 9.5 months, QTc changed from 518 ± 69 ms to 507 ± 63 ms, with nil surgical complications and reduced appropriate ICD shocks
Hwang et al.[15]	1	11 years	LCSD + PPI	At 6 months follow-up, no documented arrhythmias
Arwa et al.[16]	3	Mean age 9.3 ± 3.3 years	2 underwent LCSD 1 underwent LCSD + ICD	Mean QTc decreased from 582 ± 57 ms to 497 ± 117msec post-operatively
Index study (2021)	6	Mean age 2.75 ± 0.39 years	3 underwent LCSD, 3 underwent LCSD + PPI-AAI	At a mean follow-up of 20 months, there was reduction in QTc (603 ± 93 ms to 525 ± 41 ms) with no adverse outcomes

Abbreviations: ICD, intracardiac defibrillator; LCSD, left cardiac sympathetic denervation; PPI, permanent pacemaker implantation.

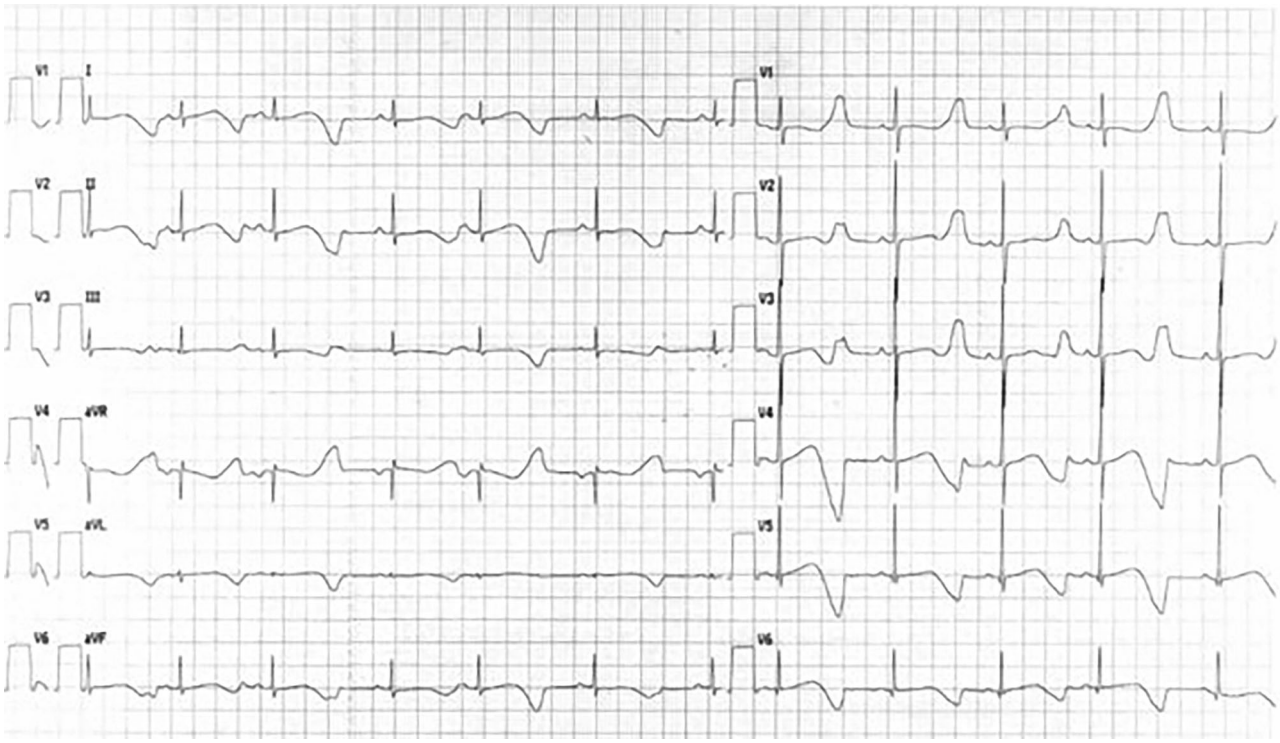

FIGURE 1 Baseline ECG showing prolonged QTc with T wave alternans.

LCSD at 39 months of age, and was continued on oral propranolol. At the last follow-up at 5 years of age, he was totally asymptomatic.

3.3 | Case 3

A 3-year boy presented with delayed language milestones and recurrent episodes of unexplained syncope since 2 years of age. Hearing evaluation showed bilateral sensorineural hearing loss. There was no family history of similar episodes or of SCD, and family screening was also negative. His ECG showed sinus bradycardia with prolonged QT interval (QTc 520 ms) and TWA.

He underwent LCSD followed by epicardial pacing, and propranolol was continued. He has been followed up till 50 months of age, and has had no further recurrence of syncope.

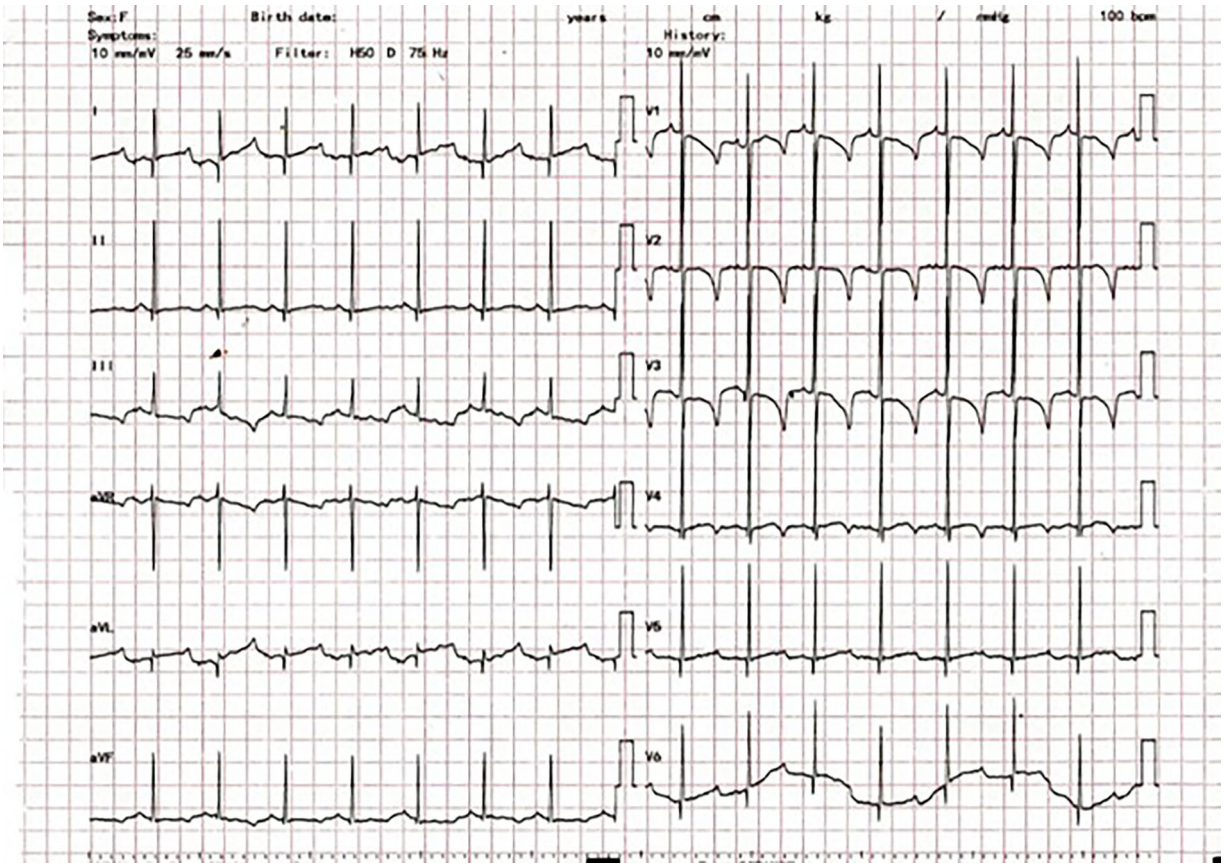

FIGURE 2 Follow-up ECG showing reduction in QTc with no T wave alternans. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Case 4

A 2 ½ year old boy was referred to our institute for recurrent breath holding spells since 2 years of age, and one episode requiring resuscitation. He had undergone cochlear implantation for bilateral sensorineural hearing loss at 9 months of age. Electrocardiogram showed prolonged QT interval (QTc 540 ms), with negative family screening.

LCSD was performed at 32 months of age and loop recorder was implanted. He was continued on oral propranolol and follow-up over the next 36 months did not reveal any adverse cardiovascular event or arrhythmia on loop recorder.

3.5 | Case 5

A 9-year-old boy with sensorineural deafness diagnosed in infancy presented with recurrent episodes of syncope since childhood exacerbated by emotional disturbances. ECG showed sinus rhythm with prolonged QT interval (QTc 550 ms) with TWA, and was started on oral propranolol. Family screening was negative (father 430 ms, mother 400 ms, and brother 320 ms). In view of recurrent symptoms, he underwent LCSD. Post-operatively he was continued on propranolol, and did not have any recurrence of syncope.

3.6 | Case 6

A 2-year-old boy presented with recurrent episodes of syncope aggravated by straining and emotional upset, along with bilateral sensorineural deafness since infancy. A 12-lead ECG showed sinus bradycardia with prolonged QTc of 640 ms with TWA. Genotyping showed KCNQ1 exon 5 homozygous mutation, along with mutations in TrioBP exon 12 and 16. In view of persistent symptoms despite being on oral propranolol with significant bradycardia, he underwent LCSD and epicardial AAI pacemaker implantation. Propranolol was continued and he did not have any recurrence of symptoms.

4 | DISCUSSION

This series of six cases is a subset of Channelopathy registry funded by Indian Council for Medical Research (ICMR). We have used oral beta blocker therapy (propranolol) as the usual mainstay of therapy in patients with LQTS. It reduces the heart rate, shortens QT interval and reduces the sympathetic effect on the heart, thereby decreasing the incidence of torsades de pointes and the risk of malignant arrhythmia.[4] Intracardiac defibrillator (ICD) implantation is recommended in patients who have high risk features or continue to have

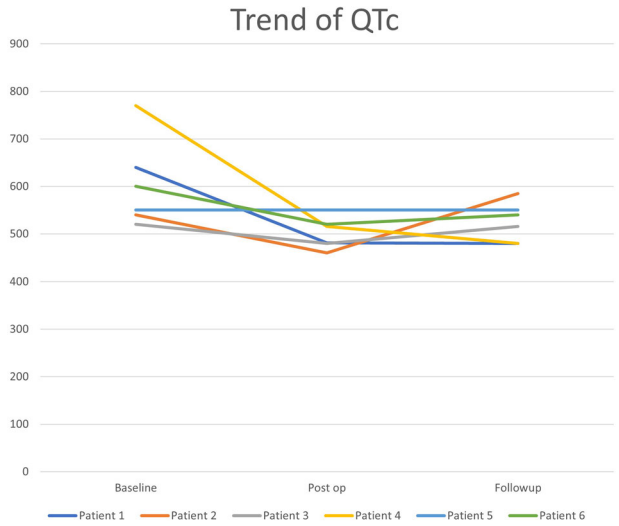

FIGURE 3 Line graph showing trend of QTc pre-operatively and on follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

symptoms despite optimal beta-blocker therapy.[5] However, implantation of ICD in children is difficult owing to their smaller body size with lack of properly sized devices.

The first report of sympathetic denervation was reported by Moss et al in 1971.[6] However, the benefit of SCD reduction was first identified by Schwartz et al in a cohort of 85 patients.[7] The standard procedure involves high thoracic left sympathectomy with ablation of the lower half or lower third of the left stellate ganglion, together with the thoracic ganglia T2 to T4.[8] It has been found to reduce episodes of sudden cardiac arrest and syncope, prolongs survival and avoids Horner's syndrome.[9] The first procedure in a child was reported by Reardon et al in 2000; similar procedures have been reported later on but majority were well over 5 years of age.[10] The youngest child to undergo this procedure has been reported by Silver et al at 3 months of age.[11] Modulation of the cardiac neural axis by LCSD has also been found effective in treating patients with PVC (premature ventricular complexes) too.[12] The efficacy of LCSD in successfully reducing the ventricular arrhythmia burden and AICD shocks in 10 patients with non-ischemic cardiomyopathy and ventricular arrhythmia resistant to drug and ablation therapy has recently been published.[13] Multiple mechanisms at neuromodulation may be functional in a given case with most of them favorably affecting the transmural dispersion of repolarization.

In our series, the mean age was only 2.75 ± 0.39 years, which is significantly less than all the previous studies (Table 2). There was a significant delay between onset of symptoms and diagnosis (mean 7.2 ± 3.5 months. All had sensorineural hearing loss, conforming to the JLN phenotype, although genetic sequencing was not available. Mean QTc duration was 603 ± 93 ms. All of them had high risk features—TWA on ECG (Figure 1) and syncope/resuscitated cardiac arrest. Family history of SCD was present in only one patient.

All were followed up for a mean period of 20 months with no evidence of significant adverse events. There was a significant reduction in QTc (603 ± 93 ms to 501 ± 33 ms, $p = .04$) (Figure 2), immediately post-operatively which was persistent on follow-up (525 ± 41 ms) (Figure 3) and only 2 had persistent T wave alternans on ECG ($p < .01$).

5 | CONCLUSION

This is one of the largest cohorts of children with JLNS who underwent LCSD from the Indian subcontinent. LCSD is associated with reduction of QTc interval and arrhythmic burden, as well as arrhythmia-free survival in all children with JLNS who have arrhythmia refractory to oral propranolol.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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