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Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy
A Randomized Clinical Trial

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IMPORTANCE The ketogenic diet (KD) has been used successfully to treat children with drug-resistant epilepsy. Data assessing the efficacy of the modified Atkins diet (MAD) and low glycemic index therapy (LGIT) diet compared with the KD are scarce.

OBJECTIVE To determine whether the MAD and LGIT diet are noninferior to the KD among children with drug-resistant epilepsy.

DESIGN, SETTING, AND PARTICIPANTS One hundred seventy children aged between 1 and 15 years who had 4 or more seizures per month, had not responded to 2 or more antiseizure drugs, and had not been treated previously with the KD, MAD, or LGIT diet were enrolled between April 1, 2016, and August 20, 2017, at a tertiary care referral center in India.

EXPOSURES Children were randomly assigned to receive the KD, MAD, or LGIT diet as additions to ongoing therapy with antiseizure drugs.

MAIN OUTCOMES AND MEASURES Primary outcome was percentage change in seizure frequency after 24 weeks of dietary therapy in the MAD cohort compared with the KD cohort and in the LGIT diet cohort compared with the KD cohort. The trial was powered to assess noninferiority of the MAD and LGIT diet compared with the KD with a predefined, noninferiority margin of −15 percentage points. Intention-to-treat analysis was used.

RESULTS One hundred fifty-eight children completed the trial: KD (n = 52), MAD (n = 52), and LGIT diet (n = 54). Intention-to-treat analysis showed that, after 24 weeks of intervention, the median (interquartile range [IQR]) change in seizure frequency (KD: −66%; IQR, −85% to −38%; MAD: −45%; IQR, −91% to −7%; and LGIT diet: −54%; IQR, −92% to −19%) was similar among the 3 arms (P = .39). The median difference, per intention-to-treat analysis, in seizure reduction between the KD and MAD arms was −21 percentage points (95% CI, −29 to −3 percentage points) and between the KD and LGIT arms was −12 percentage points (95% CI, −21 to 7 percentage points), with both breaching the noninferiority margin of −15 percentage points. Treatment-related adverse events were similar between the KD (31 of 55 [56.4%]) and MAD (33 of 58 [56.9%]) arms but were significantly less in the LGIT diet arm (19 of 57 [33.3%]).

CONCLUSIONS AND RELEVANCE Neither the MAD nor the LGIT diet met the noninferiority criteria. However, the results of this study for the LGIT diet showed a balance between seizure reduction and relatively fewer adverse events compared with the KD and MAD. These potential benefits suggest that the risk-benefit decision with regard to the 3 diet interventions needs to be individualized.

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Supplemental content

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The International League Against Epilepsy defines drug-resistant epilepsy as "failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[1(p28)] Drug-resistant epilepsy responds poorly to pharmacologic management and frequently requires intervention via other modalities, including surgery, vagus nerve stimulation, and dietary therapy. However, standards of care for drug-resistant epilepsy management have not been well defined. In addition, the coexistent motor, language, and memory deficits may render some patients unsuitable for curative epilepsy surgery.

Dietary therapies have been reported to be effective and safe, and can be administered synergistically with other treatment options.[2] The classic ketogenic diet (KD) is a high-fat, adequate protein, low-carbohydrate diet. The KD has been shown to be effective in randomized clinical trials, and benefits have been reported across various retrospective and prospective observational studies.[3,4] However, some families and patients find adherence to the KD difficult, and it has an established adverse effect profile.[5] Therefore, other diets, such as the modified Atkins diet (MAD) and low glycemic index therapy (LGIT) diet, have been investigated.[6,7] Results from various studies have indicated that the MAD is as effective as the KD for drug-resistant epilepsy management, but the evidence is limited.[6,8]

In 2018, the International Ketogenic Consensus Guideline stated that the diet should be "individualized based on the family and child situation, rather than perceived efficacy,"[2(p181)] and that there was reasonable class III evidence to support its use. However, a Cochrane review, which included 7 randomized clinical trials assessing the efficacy of the KD in drug-resistant epilepsy, concluded that other more palatable diets "may have a similar effect on seizure control as classical KD but this assumption requires more investigation."[9(p2)] This randomized trial was undertaken to assess whether addition of either the MAD or LGIT diet to ongoing antiseizure drug therapy was noninferior to the KD with regard to seizure reduction at 24 weeks among children aged 1 to 15 years with drug-resistant epilepsy.

Key Points

Question Are the modified Atkins diet and low glycemic index therapy diet noninferior to the ketogenic diet with regard to seizure reduction at 24 weeks among children aged 1 to 15 years with drug-resistant epilepsy?

Findings In this randomized clinical trial of 158 children with drug-resistant epilepsy, the median reduction in seizure burden was similar between the ketogenic diet, modified Atkins diet, and low glycemic index therapy diet, although the noninferiority of the modified Atkins diet and low glycemic index therapy diet was not proven. The adverse events were least with the low glycemic index therapy diet, and 1 adverse event may be avoided for every 4.3 children treated with the low glycemic index therapy diet compared with a ketogenic diet.

Meaning The findings of this trial indicate that guidelines should support the use of the ketogenic, modified Atkins, and low glycemic index therapy diets for management of drug-resistant epilepsy; each dietary therapy should be discussed with caregivers in terms of the benefit in reducing seizure burden and the risk of adverse events.

Methods

Study Design

This noninferiority randomized clinical trial was conducted at All India Institute of Medical Sciences, New Delhi, India, between April 1, 2016, and August 20, 2017. The trial protocol was approved by the All India Institute of Medical Sciences Institutional Ethics Committee. Written informed consent was obtained from caregivers of participating children. Children between age 1 and 15 years with drug-resistant epilepsy presenting to the pediatric neurology outpatient clinic were considered for inclusion. Drug-resistant epilepsy was defined as seizure frequency of 4 or more seizures per month and treatment failure of 2 or more prescribed antiseizure drugs in maximum tolerated doses.[8] For West syndrome, drug-resistant epilepsy was defined as more than 4 spasm clusters per month despite treatment with 2 or more antiseizure drugs and either adrenocorticotropic hormone or vigabatrin. Exclusion criteria included surgically remediable cause of drug-resistant epilepsy, inborn errors of metabolism, and known chronic systemic disorder. Children treated with the KD, MAD, or LGIT diet in the past were also excluded. A detailed study protocol is presented in Supplement 1. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for equivalence and noninferiority trials.

Enrolled children underwent a 4-week run-in period. During the run-in period, baseline investigations were undertaken, and syrups were reformulated to tablets that were then ground and either sprinkled over food or mixed with water to facilitate ingestion by young children. Parents were advised to maintain a daily seizure log. Demographic data and medical history were chronicled. Changes to the child's diet were not advised during the run-in period. No changes in antiseizure drug dosages were made during the run-in period or during the 24-week intervention phase. Following the run-in period, children were randomly assigned to 1 of 3 interventions: KD, MAD, or LGIT diet. Computer-generated, random, permuted blocks stratified by age (1-5, >5-10, and >10-15 years) were used to generate a randomization list. Sealed and serially numbered opaque envelopes were used for allocation concealment. The dietitian and one of us (V.S.) directly involved with diet prescription could not be blinded to treatment. Participants, other study personnel, and those who analyzed the data were blinded.

Tailored diet prescriptions were developed for each patient based on food preferences and staple diet of the family. A gradual-initiation, nonfasting protocol was used for introducing the KD, which involved administering 75% of total daily caloric requirement on the day of the KD initiation and gradually increasing it to full calorie level over 2 to 4 weeks, as tolerated by the child.[10] Classic KD was started at a 1:1 ratio (lipids: nonlipids). Lipid content was gradually increased to 2:1, 2.5:1,

3:1, and 4:1 every 48 hours while urinary ketosis and tolerance were monitored. The MAD group patients followed the Johns Hopkins protocol.[11] Initiation of the LGIT diet involved restricting high glycemic index (>55) food items and limiting carbohydrates to approximately 10% of daily calories. All families were educated about the diet and provided with a detailed menu plan. The MAD and LGIT diets were started in the outpatient setting, while children were admitted for initiating the KD. For the MAD and LGIT diets, a list of food replacement options was also provided. Diets were supplemented with vitamins and minerals. Each patient's caregiver maintained a daily log of meals, seizure frequency, urinary ketones, and dietary intolerance symptoms. Patients were followed up as outpatients at 4, 12, and 24 weeks after intervention initiation. Twice-weekly telephone calls were made to ensure dietary adherence, monitor for adverse events, and address any caregivers' concerns.

Seizure frequency was assessed from the daily log (eAppendix 1 in Supplement 1). Mean and median number of seizures at a time point were calculated from seizure counts in the preceding 28 days and expressed as percentage change from baseline. Diet tolerance and adverse events were evaluated in interviews with caregivers. Evaluation details performed at each hospital visit are reported in eAppendix 2 and eAppendix 3 in Supplement 1. Serum was isolated within 2 hours of blood sample collection at baseline and at 24 weeks and stored at −80 °C. Levels of copper, selenium, and zinc in all serum samples were measured in a single batch.

The primary outcome was percentage change in seizure frequency from baseline at 24 weeks of therapy. The primary outcome measure was assessed in a blinded manner; daily logs were coded with unique identification numbers and assessed by an individual (R.M.P.) blinded to intervention. Secondary outcomes, which were analyzed 24 weeks after intervention initiation, included proportion of patients with greater than 50% seizure reduction from baseline, proportion of patients showing improvement in social quotient on the Vineland Social Maturity Scale (scores of 85-110 considered normal; higher scores, higher levels of function),[12] changes in T score on the Child Behavior Checklist (normal score, <60; borderline, 60-63; and clinically impaired, >63),[13] and changes in serum levels of copper, selenium, and zinc. Urinary ketone levels, recorded by parents as numeric values of 0 to 4 on urinary dipstick, were used to assess the level of ketosis. The median urinary ketone level over the past 4 weeks was associated with mean and median percentage decline in seizure frequency. The rate of seizure decline was calculated for each week using the formula $100 \times (y - x)/x$, where y indicates the mean or median number of daily seizures in the preceding week and x indicates the mean or median baseline number of daily seizures during run-in. Adherence to the prescribed diet was assessed from daily logs, which included the number of meals given and portions left uneaten. The proportion of prescribed diet that was consumed was computed every 4 weeks. A minimum 80% value was required for inclusion in the final analysis.

Sample size calculations were based on the study by Kim et al,[8] who reported that, after 6 months of the KD and MAD, the KD group had 33.8% and the MAD group had 44.6% of baseline seizure frequency. Guided by this 10.8-percentage point difference, the predetermined noninferiority margin was set at a 15-percentage point difference between the treatment arms. Testing for this margin with 80% power at an α level of .05, assuming an SD of 30% for outcomes after 24 weeks of treatment, requires 50 patients per group. Assuming a 10% dropout rate, the required sample size was 165.

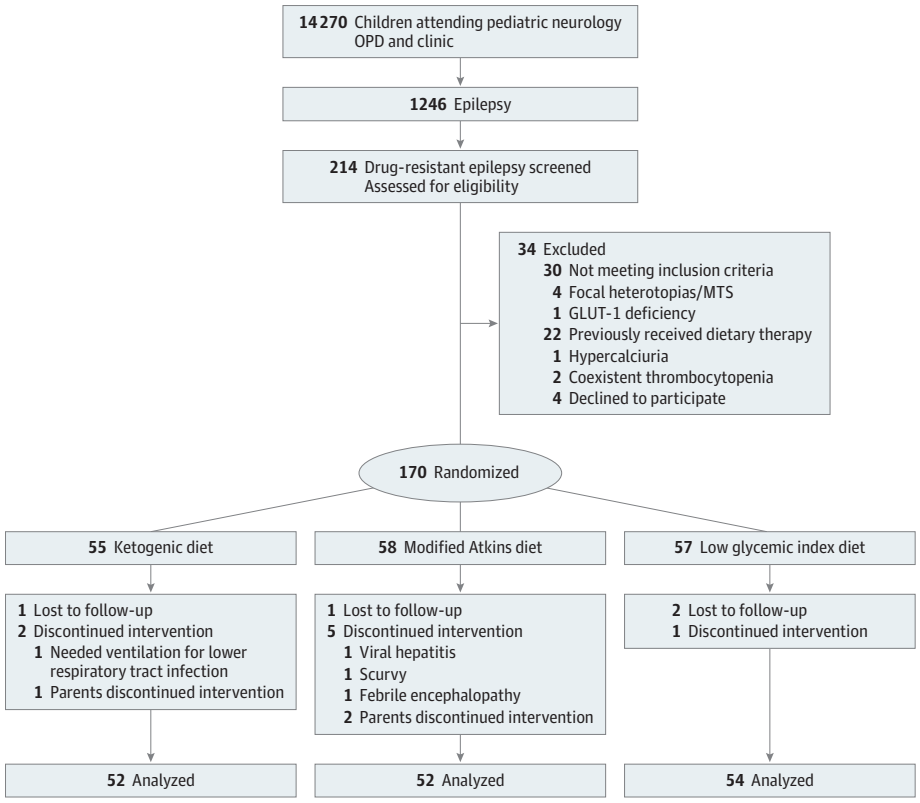
Statistical Analysis

The primary outcome of percentage seizure reduction at 24 weeks was analyzed by computing the effect size (mean or median difference) and determining its 95% CI. The MAD and LGIT diet were considered noninferior to the KD when the lower limit of the 95% CI of effect size was greater than −15 percentage points. Results were checked for distribution normality, and mean or median values were used as appropriate. The intention-to-treat (ITT) population included all patients who fulfilled eligibility criteria and were assigned an intervention. With ITT analysis, for patients who could not be contacted at 24 weeks of intervention, the number of mean or median daily seizures over the last 4 weeks of last contact with the patient was used for primary end-point calculation. The per-protocol population was defined to exclude randomly assigned patients who did not receive the full allocated treatment up to 24 weeks. For secondary outcomes, the intervention groups were compared using the χ^2 test or Fisher exact test for categorical variables and standard unpaired, 2-tailed t test or Wilcoxon-Mann-Whitney test for continuous variables. P values <.05 were considered statistically significant. Adverse events were summarized per treatment group and compared as proportions with a χ^2 test. Statistical analysis was conducted using R, version 3.5.1 (R Foundation).

Results

Of 214 children with drug-resistant epilepsy who were screened, 170 were randomly assigned to receive the KD (n = 55), MAD (n = 58), or LGIT diet (n = 57) and were included in ITT analysis (**Figure 1**). Twelve patients were withdrawn, and the remaining 158 patients (KD, 52; MAD, 52; and LGIT diet, 54) were included in per-protocol analyses. Their baseline characteristics are shown in **Table 1**. The 3 groups were similar for median baseline daily seizures (KD, 9; MAD, 8.5; and LGIT diet, 9; P = .99), proportion of patients with structural epilepsy (KD, 33; MAD, 41; and LGIT diet, 41; P = .33), and proportion of patients requiring 4 or more antiseizure drugs (KD, 20; MAD, 31; and LGIT diet, 31; P = .16). Baseline clinical examination was normal in 9 patients (16.4%) receiving a KD compared with 2 children (3.4%) receiving an MAD and 2 children (3.5%) receiving an LGIT diet (P = .01). Details of drug-resistant epilepsy causes and antiseizure drug use are given in eAppendix 4 and eAppendix 5 in Supplement 1, respectively. Mean (SD) dietary adherence was significantly better with the LGIT diet (94.3% [2.6%]) compared with the KD (91.4% [2%]) or MAD (90.6% [2.4%]). All patients had greater than 80% adherence throughout the study (eAppendix 6 in Supplement 1).

Figure 1. Flow of Patients



GLUT-1 indicates glucose transporter type 1; MTS, mesial temporal sclerosis; and OPD, outpatient department.

Outcomes

Twenty-four weeks after intervention, the median daily seizure frequency was 3.3 (interquartile range [IQR], 1.2-14) with the KD, 4 (IQR, 0.5-10) with the MAD, and 4 (IQR, 0.4-11) with the LGIT diet (**Table 2**). After 24 weeks of intervention, the median change in seizure frequency was similar among the 3 arms in both the ITT (KD: −66%; IQR, −85% to −38%; MAD: −45%; IQR, −91% to −7%; and LGIT diet: −54%; IQR, −92% to −19%; $P = .39$) and per-protocol populations ($P = .57$) (Table 2). The median difference in change in seizure frequency between the KD and MAD was −21 percentage points (95% CI, −29 to −3 percentage points) in ITT and −10 percentage points (95% CI, −26 to 5 percentage points) in per-protocol analysis. The median difference in change in seizure burden between the KD and LGIT diet was −12 percentage points (95% CI, −21 to 7 percentage points) in ITT analysis and −7 percentage points (95% CI, −17 to 10 percentage points) in per-protocol analysis (**Table 3**).

Proportions of patients with greater than 50% seizure reduction at 24 weeks were comparable across the 3 arms: KD, 35 of 52 (67.3%); MAD, 27 of 52 (51.9%); and LGIT diet, 32 of 54 (59.3%). The odds ratio (OR) between KD and MAD was 0.16 (95% CI, 0.86-4.22); between KD and LGIT diet, 1.42 (95% CI, 0.64-3.13); and between MAD and LGIT diet, 0.74 (95% CI, 0.34-1.60) (**Figure 2**). The change in seizure frequency was not associated with urinary ketone levels (eAppendix 7 in Supplement 1). There was rapid seizure reduction over the initial 4 weeks of the study with the KD and MAD, while the decrease was gradual over 10 to 12 weeks with the LGIT diet (eAppendix 8 in Supplement 1). Post hoc subgroup analysis by age (1-5, >5-10, and >10-15 years) was performed for percentage reduction in seizures and proportion of children with greater than 50% seizure reduction. All subgroups were comparable for reduction in seizure burden between the 3 interventions (eAppendix 9 in Supplement 1). At 24 weeks after the intervention, the mean social quotient improved in 83 children (54.2%) (eAppendix 10A in Supplement 1). The improvement was most notable with the KD (34 of 52 [65.4%]) followed by the LGIT diet (29 of 54 [53.7%]) and MAD (20 of 52 [38.5%]) ($P = .02$). After 24 weeks, the change in mean total T score was nonsignificant and similar for the 3 interventions (eAppendix 10B in Supplement 1).

Adverse Events

Adverse events noted among 83 of 170 patients (48.8%) were comparable between the KD (31 of 55 [56.4%]) and MAD (33 of 58 [56.9%]) but were significantly less with the LGIT diet (19 of 57 [33.3%]) (eAppendix 11 in Supplement 1). The commonest clinical adverse event was vomiting, which was noted in 28 patients (50.9%) receiving the KD, 26 patients (44.8%) receiving the MAD, and 18 patients (31.6%) receiving the LGIT diet (eAppendix 12 in Supplement 1). Investigation-based adverse events were reported in 59 patients (34.7%) (KD, 21 [38.2%]; MAD, 24 [41.4%]; and LGIT diet, 14 [24.6%]; $P = .14$). Two patients receiving the LGIT diet and 1 patient receiving the KD were noted to have thrombocytopenia during evaluation at 24 weeks. Both patients were also receiving sodium val-

Table 1. Demographic and Clinical Characteristics at Baseline

Variable	No. (%)		
	KD (n = 55)	MAD (n = 58)	LGIT diet (n = 57)
Age, mo			
Mean (SD)	62.2 (38.1)	62.3 (40.2)	63.8 (37.0)
Median (IQR)	52 (31-89)	51 (31-79)	54 (32.5-82)
Male sex	37 (67.3)	49 (84.5)	42 (73.7)
Diagnosis			
Structural epilepsy	33 (60.0)	41 (70.7)	41 (71.9)
Genetic epilepsy	16 (29.1)	12 (20.7)	14 (24.6)
Genetic epilepsy with structural abnormality	6 (10.9)	5 (8.6)	2 (3.5)
Age at first seizure, mo			
Mean (SD)	6.74 (11.46)	9.5 (21.03)	9.19 (18.92)
Median (IQR)	2 (0-8)	2 (0-8)	0 (0-8.5)
Type of seizure at enrollment			
Spasms	33 (60.0)	41 (70.7)	38 (66.7)
Myoclonic (other than spasms)	26 (47.2)	23 (39.7)	21 (36.8)
Tonic	31 (56.4)	33 (56.9)	39 (68.4)
GTCS	3 (5.5)	3 (5.2)	1 (1.8)
Focal	10 (18.2)	11 (18.9)	17 (29.8)
Absence	13 (23.6)	14 (24.1)	13 (22.8)
Multifocal	31 (56.3)	35 (60.3)	41 (71.9)
Antiepileptic drugs			
2-3	35 (63.6)	27 (46.6)	26 (45.6)
≥4	20 (36.4)	31 (53.4)	31 (54.4)
Median (IQR)	3 (3-4)	4 (3-4)	4 (3-4)
Developmental delay			
GM	41 (74.5)	46 (79.3)	43 (75.4)
FM	44 (80.0)	49 (89.1)	49 (85.9)
Language	50 (90.9)	50 (86.2)	52 (91.2)
Sociocognitive	51 (92.7)	52 (89.7)	54 (94.7)
Clinical examination			
Normal	9 (16.4)	2 (3.4)	2 (3.5)
Pyramidal signs	36 (65.5)	43 (74.1)	45 (78.9)
Extrapyramidal signs	10 (18.2)	13 (22.4)	10 (17.5)
Cranial nerve palsy	13 (23.6)	17 (29.3)	12 (21.1)
Baseline daily seizures			
Mean (SD)	20.2 (25.1)	20 (29.3)	20.1 (38.7)
Median (IQR)	9 (6-19)	8.5 (5-20)	9 (4.5-19.5)

Abbreviations: FM, fine motor; GM, gross motor; GTCS, generalized tonic clonic seizures; IQR, interquartile range; KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

proate. Ten patients, all receiving concomitant zonisamide therapy, were found to have hypercalciuria at 24 weeks. In addition, 2 patients receiving the MAD developed scurvy, detected at 24 weeks in one child and at 12 weeks in the other, who was withdrawn from the study. Both of these children presented with extreme irritability and incessant crying. Owing to unavailability of resources for serum vitamin C assay, the diagnosis of scurvy was based on characteristic radiologic findings and clinical response to vitamin C therapy.

Three patients developed a prolonged QTc interval. For 2 of these children, the prolonged interval was detected at 24 weeks' assessment, while for the third patient, the observation was made following hospital admission for respiratory tract infection, which necessitated diet discontinuation. The baseline QTc intervals for these 3 patients were 0.30, 0.31, and 0.36 seconds; following intervention, the intervals were 0.51, 0.54, and 0.52 seconds. Serum samples were additionally tested for zinc, selenium, and copper levels; preintervention and postintervention comparisons are provided in eAppendix 13 in Supplement 1. Children receiving the KD and MAD had significant decreases in their serum selenium levels, although the levels remained within the reference range. Preintervention/postintervention and intergroup anthropometric comparisons did not show any statistically significant differences (eAppendix 14 in Supplement 1).

Discussion

In this randomized clinical trial involving children with drug-resistant epilepsy, the MAD and LGIT diets were not noninferior to the KD with respect to seizure reduction at 24 weeks

Table 2. Seizure Frequency

Variable	No. (%)		
	KD (n = 52)	MAD (n = 52)	LGIT diet (n = 54)
Seizure frequency at 24 wk			
Median (IQR)	3.3 (1.2 to 14)	4 (0.5-10)	4 (0.4-11)
Mean (SD)	9.4 (14)	11 (19)	8.7 (12)
Achieved specific cutoff points after 24 wk of intervention			
Complete resolution	6 (11.5)	8 (15.4)	9 (16.7)
>90% Reduction	6 (11.5)	6 (11.5)	8 (14.8)
>50% Reduction	23 (44.2)	13 (25.0)	15 (27.8)
≤50% Reduction	13 (25.0)	14 (26.9)	15 (27.8)
Increase in seizure frequency at 24 wk	4 (7.7)	11 (21.2)	7 (12.9)
% Change in seizure frequency			
Per-protocol analysis			
Median (IQR)	−67 (−87 to −37)	−57 (−92 to −5.5)	−60 (−92 to −24)
Mean (SD)	−60 (33)	−48 (46)	−55 (40)
Intention-to-treat analysis			
Median (IQR)	−66 (−85 to −38)	−45 (−91 to −7)	−54 (−92 to −19)
Mean (SD)	−60 (32)	−46 (45)	−52 (41)

Abbreviations: IQR, interquartile range; KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

Table 3. Difference in Seizure Reduction With the 3 Treatment Strategies[a,b]

Comparison between interventions	Per-protocol analysis		Intention-to-treat analysis	
	Median (95% CI)	Mean (95% CI)	Median (95% CI)	Mean (95% CI)
KD-MAD	−10 (−26 to 5)	−12 (−28 to 3.2)	−21 (−29 to 3)	−14 (−28 to 0.61)
KD-LGIT	−7 (−17 to 10)	−5.7 (−20 to 8.4)	−12 (−21 to 7)	−8.1 (−22 to 5.5)

Abbreviations: KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

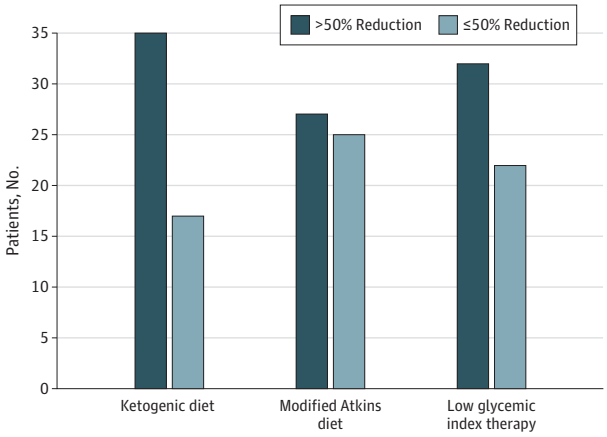
[a] In both the per-protocol and intention-to-treat analyses, the lower limit of the 95% CI of the median difference and mean difference in seizure reduction between MAD and KD, as well as between LGIT diet and KD, breached the noninferiority margin of −15 percentage points.

[b] Data are given as percentage points.

after diet initiation. In ITT analysis, median seizure reductions were 66% for the KD, 45% for the MAD, and 54% for the LGIT diet. The median difference in seizure frequency between the MAD and KD (−21 percentage points; 95% CI, −29 to 3 percentage points) and between the LGIT diet and KD (−12 percentage points; 95% CI, −21 to 7 percentage points) both breached the noninferiority limit of −15 percentage points. Hence, the trial failed to demonstrate that the LGIT diet or MAD is noninferior to the KD in children with drug-resistant epilepsy. However, the proportions of patients with greater than 50% seizure reduction at 24 weeks were similar across the 3 diets.

Our results should be interpreted in 5 main aspects that go beyond the noninferiority domain. First, this trial addressed the treatment strategies in terms of seizure reduction at a given time, expressed as percentage change with respect to baseline seizures. Most previous literature expresses the outcomes as proportions of patients with greater than 50% seizure reduction.[3,7,14] Our approach gives a more absolute seizure reduction with each strategy. The proportion of children with greater than 50% seizure reduction after 24 weeks of the interventions was 67.3% with the KD, 51.9% with the MAD, and 59.3% with the LGIT diet. To put things into perspective, the median number of daily seizures at the beginning of the trial was nearly 9 per day per group. After 24 weeks of intervention, the per-day seizure burden had decreased to 3 with the KD and 4 with both the MAD and LGIT diet. For the subsequent analysis, a noninferiority margin of −15 percentage points implied a difference of nearly 1 to 2 seizures per day for a child having nearly 9 seizures per day at the start of the study. Both the MAD and LGIT diet were not noninferior to the KD as the lower limit of the 95% CI of effect size crossed the margin of −15 percentage points. The seizure reduction noted with the KD and LGIT diet is comparable with published reports; however, the present study demonstrated lesser reduction of seizures with the MAD.[3,7,8,14] This difference can be partially accounted for by the fact that a diet was started late in the clinical course in our study, probably rendering the patients more drug resistant. The differences in seizure reduction with 3 interventions can be partly accounted for by the type of patients in each arm. Nine patients in the KD group had a normal neurologic examination compared with 2 each in the MAD and LGIT diet groups (P = .01). In addition, 20 patients in the KD group required 4 or more antiseizure drugs compared with 31 patients in both of the other groups. This difference may suggest that the patients in the MAD and LGIT diet groups had more refractory causes of seizures than those in the KD group.

Figure 2. Numbers of Patients With Greater Than 50% Reduction vs 5% or Less Reduction in Daily Seizure Frequency 24 Weeks After Intervention



Proportions of patients with greater than 50% reduction in seizure frequency with ketogenic diet, modified Atkins diet, and low glycemic index therapy diet were comparable between ketogenic diet and modified Atkins diet (odds ratio [OR], 1.42; 95% CI, 0.64-3.13), between KD and MAD (OR, 0.16; 95% CI, 0.86-4.22), and between MAD and LGIT diet (OR, 0.74; 95% CI, 0.34-1.60).

Second, the daily seizure log allowed for assessment of the rate of decline in seizures with each intervention. Administration of the KD was associated with an approximate 50% decline in seizure frequency in the first 4 weeks, and a further 10% reduction in seizure frequency was noted over the subsequent 20 weeks. Seizure reduction with the MAD was also rapid, with an approximate 40% decrease in the number of seizures by 4 weeks; seizure frequency plateaued between 40% and 50% over the next 20 weeks. With the LGIT diet, however, the seizure decline was gradual, with 50% reduction attained between 10 and 12 weeks. This understanding is necessary before a patient is considered to be a nonresponder and also to give a realistic perspective to caregivers. The rate of decline was considerably more rapid with the lipid-rich KD and MAD compared with the LGIT diet, which is primarily associated with restriction of carbohydrates to low glycemic index foods. While the KD and MAD are associated with ketosis, the exact role of ketone bodies in seizure control is unclear. Some animal studies have suggested that acetoacetate might reduce glutamate release at hippocampal synapses, while other studies have failed to show any association between ketone bodies and synaptic transmission.[15-17] Studies have suggested an association between seizure control and serum levels of β-hydroxybutyrate.[18] We measured urinary ketone levels and failed to show any association with change in seizure frequency, although serum ketone level estimation might have been more appropriate.

Third, this study assessed the effect of dietary strategies on drug-resistant epilepsy as a complete group and not etiologic or syndromic subcategories, which increases the generalizability of results and captures the complexity of clinical practice. Most enrolled children had spasms or generalized or multifocal seizures. The children with focal epilepsy were underrepresented because most children with lesional focal epilepsy were candidates for epilepsy surgery and, hence, were excluded from the study.

Fourth, this study demonstrated an improvement in social quotient with all 3 interventions; this improvement was statistically significantly better with the KD compared with the MAD, while the response was comparable between the KD and LGIT diet, as well as between the MAD and LGIT diet. In a randomized clinical trial assessing the cognitive and behavioral effect of the KD in children and adolescents with drug-resistant epilepsy, participants receiving the KD had lower levels of anxious and mood-disturbed behavior.[19] To our knowledge, there are no comparable studies for MAD and LGIT diet interventions. Although the delineation of mechanisms explaining the improvement in social quotient is beyond the scope of this study, the improvement in social quotient can be partly attributed to the reduced seizure burden with each of the interventions. The change in the T score was not significant in our trial, and it is possible that the 24-week interval of observation was too brief to observe a change in this measure.

Fifth, all interventions were associated with adverse events. The KD and MAD were associated with poor dietary tolerance with vomiting, difficulties with palatability, diarrhea, and constipation.[3,6,14] In addition, lipid profiles in these patients were altered owing to prolonged ingestion of high-lipid diets. Nephrocalcinosis and increased urinary calcium excretion in patients receiving the KD and MAD can be related to fat malabsorption and chronic acidosis, partly attributable to concurrent zonisamide therapy. In contrast, the LGIT diet was associated with minimal adverse events, none of which was life threatening. These reduced adverse events associated with the LGIT diet suggest a trade-off between the efficacy and harmful effects of the intervention. Although the risk-benefit trade-off was not considered at the beginning of the intervention, our results suggest that the LGIT diet led to lesser seizure reduction than the KD (average difference of approximately 1 seizure per day). However, absolute risk reduction of adverse events was approximately 23% among study participants treated with the LGIT diet compared with children receiving the KD. Hence, 1 adverse event can be avoided for every 4.3 children treated with the LGIT diet compared with the KD.

Strengths and Limitations

The strengths of our study are its embedment within the clinical practice setting with the inclusion of all children with drug-resistant epilepsy, irrespective of the underlying cause, allowing for generalizability of its results. To our knowledge, this is the first trial to analyze the 3 primary dietary options for drug-resistant epilepsy—KD, MAD, and LGIT diet—for seizure reduction, adverse events, and cognitive effects. The dropout rate of less than 10% in each of the 3 arms and dietary adherence greater than 80% further strengthen the results.

The trial also has limitations. The scientific weight of the study would have been better if the SD in each cohort was smaller. However, this was a close representation of a clinical setting with different drug-resistant forms of epilepsy responding to different degrees and at different rates. The study would also have been improved by blinding all involved individuals. However, it was impossible to blind dietitians, as the diet pre-

scriptions required close parental interaction. The use of daily logs maintained by caregivers would have missed some seizures, including nocturnal seizures, and runs the risk of introducing subjective errors. In addition, a selection bias cannot be ruled out because this was a single-center study.

Conclusions

The data from this study show that all 3 dietary regimens—KD, MAD, and LGIT diet—significantly reduce the seizure burden in children with drug-resistant epilepsy. This information supports the use of all 3 dietary therapies. Still, the results are inconclusive with regard to noninferiority of the MAD and LGIT diet. The risk profiling illustrates that the LGIT diet is associated with the least number of and least severe adverse events, while the other 2 diets are more likely to be associated with serious and life-threatening events. It appears that each dietary intervention should be assessed in terms of the benefit in reducing seizure burden and the risk of adding adverse events before starting the KD, MAD, or LGIT diet in children.

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PLOS ONE

RESEARCH ARTICLE

Development and validation of DSM-5 based diagnostic tool for children with Autism Spectrum Disorder

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Abstract

Diagnostic and Statistical Manual of mental disorder-IV (DSM-IV) TR based INCLEN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD) is an established instrument for the diagnosis of ASD in Indian subcontinent and low-middle income countries (LMIC). The introduction of DSM-5 necessitated revision of existing INDT-ASD tool to incorporate the DSM-5 related changes. This study was undertaken to develop and validate the DSM-5 based All India Institute of Medical Sciences (AIIMS)-Modified-INDT-ASD Tool. The modifications were done using Delphi method and included: (a) rearrangement of questions from the previous tool; and (b) addition of new questions on sensory symptoms. The modified tool was validated against DSM-5 diagnostic criteria. In addition, receiver operating characteristic (ROC) curves were used to determine the cut-off for total score as compared to Childhood Autism Rating Scale (CARS) score to grade the severity of ASD. Two-hundred-twenty-five children (159 boys, median age = 47months) were enrolled. The modified tool demonstrated sensitivity of 98.4% and specificity of 91.7% to diagnose ASD. A score $\geq$14 on the tool was suggestive of severe ASD (CARS>36.5) with a sensitivity and specificity of 80% and 80.7% respectively [Area under the curve = 0.89]. AIIMS-Modified-INDT-ASD Tool is a simple and structured instrument based on DSM-5 criteria which can facilitate diagnosis of ASD with acceptable diagnostic accuracy.

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders that are characterized by deficits in two core domains: (a) impairments in social interaction and communication; and (b) restricted, repetitive behavior (RRB)[1]. Autism, Asperger's syndrome and Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS) are neurodevelopmental disorders characterized by varying degrees of impairments in social interaction, communication

and repetitive behaviors and interests. These disorders lie on a continuum of severity and diagnostic criteria overlap to a great extent[2]. These aforementioned disorders were separately defined in Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). However, with DSM-5, a single diagnosis, "Autism Spectrum Disorder", has replaced the previous subtypes. In addition, in the previous edition of DSM (DSM-IV-Text Revision (TR)) communication and socialization were separate domains; DSM-5 has integrated these to form "deficits in social communication and social interaction" resulting in a two-symptom cluster model[1].

Several diagnostic tools are available to facilitate the diagnosis of ASD. Many of them follow rigid administration standards that may be obtainable only in research setting and some require extensive training[3, 4]. In addition, the expense involved with some of these tools undermines their use in lower-middle-income countries (LMIC). In order to overcome these shortcomings, International Clinical Epidemiology Network validated DSM-IV-TR based INCLEN-Diagnostic-Tool for ASD (INDT-ASD)[5]. The tool demonstrated good psychometric properties and became widely used across Indian subcontinent and other LMIC.

However, with the transition from DSM-IV to DSM-5, and the relative paucity of DSM-5 based diagnostic tools, the INDT-ASD tool required an update. This study was undertaken to: (a) modify existing INDT-ASD tool to incorporate the DSM-5 based criteria and formulate All India Institute of Medical Sciences (AIIMS) Modified INDT-ASD tool; and (b) validate the modified tool against DSM-5 (gold standard).

Methods

Participants

The study was conducted at a tertiary care referral hospital of North India between Apr 2015 and Dec 2015. Children aged 1–14 years with "suspected ASD" were enrolled. Suspected ASD was considered when one of following features was present[6]: (a) no babbling or pointing or other gesture by 12 months; (b) no single words by 16 months; (c) no 2-word spontaneous (not echolalic) phrases by 24 months; or (d) loss of language or social skills at any age. As per American Academy of Neurology and Child Neurology Society, such children require further developmental assessment and screening for ASD. The study was approved by the Institutional Ethical Committee, All India Institute of Medical Sciences, New Delhi.

Outcome measures

This study was undertaken to develop and validate the AIIMS Modified INDT-ASD Tool, against DSM-5 based expert diagnosis, in children aged 1–14 years. The primary outcome was to assess the psychometric property of the aforementioned tool (accuracy and correlation with CARS score). Secondary outcome was development of severity scoring for ASD in this tool.

Development of AIIMS modified INDT ASD tool for ASD

A team of Paediatric neurologists, clinical psychologists and psychiatrist reviewed clinical criteria for ASD as presented in DSM-5, ICD-10, DSM-IV TR, CARS and INDT-ASD tool. Subsequently, questions from INDT-ASD tool (12 items– 4 each in social interaction, social communication, and RRBs) were selected and rearranged into seven items (three for social interaction/ communication and four for RRBs). Additional questions for sensory symptoms were pooled and reviewed by a team of experts using modified Delphi Technique. These pooled questions were rank-ordered and further reduced using endorsement rate approach. In this process, 5 questions from INDT-ASD tool were dropped and 4 new questions (sensory

symptoms) were added. Key differences in diagnostic criteria for autistic disorder and ASD using DSM-IV and DSM-5 based tools are illustrated in Table 1. The AIIMS modified INDT-ASD tool has been illustrated as supporting information (S1 File).

Components of AIIMS modified INDT ASD tool

The modified tool has two sections (Section A and Section B). Section A has 28 questions for 7 items (3 items for social interaction/communication and 4 items for RRBs); representing domains of DSM-5 criteria for ASD diagnosis. Section A has 2 subsections: Subsection A1 has three subdomains namely, deficits in social-emotional reciprocity (A1a;8 questions), non-verbal communication (A1b;4 questions) and deficits in developing and maintaining relationships (A1c; 3 questions) and subsection A2 has 4 subdomains namely- Stereotyped movements or speech (A2a;7 questions), Fixed routines (A2b;1 question), Fixed interests (A2c;1 question) and Sensory symptoms (A2d;4 questions).

Response to each question is marked as "yes", "no" or "unsure". Response of unsure is marked only when both parents and investigator (based on observation) are unsure of the response. Investigator assessment relies upon interview of primary caregivers and direct observation of child involved in spontaneous play activity. For any discrepancy in parental response and investigator's assessment, it is indicated for each question whether parental response or assessor's observation should take precedence. Based on question and indication in the tool, the response of either "yes" or "no" might be "abnormal". Number of "abnormal" responses are calculated as "total score" for each patient. Hence a child may score anywhere between zero to 28.

Section B has 9 questions for analysis of items in section A. All three subsections of section A1 (A1a, A1b, A1c) along with at least 2 out of 4 subsections of section A2 (A2a, A2b, A2c, A2d) must be "abnormal" to qualify for the diagnosis of ASD. In addition, Section B has two mandatory items- onset in early developmental period and impairment in daily functioning that is a prerequisite for diagnosis of ASD.

Pilot testing

All investigators participating in the trial underwent training for application of the tool. The training, that took four hours, was performed using lectures and by practical application of

Table 1. Key differences in diagnostic criteria for autistic disorder (DSM IV based INDT ASD tool) and ASD DSM-5 based AIIMS modified INDT ASD tool.

Parameter	DSM-IV based INDT ASD tool	DSM-5 based AIIMS modified INDT ASD tool
Social interaction	4 Subdomain (A1a, A1b, A1c, A1d)	3 Subdomain (A1a, A1b, A1c)
Social communication	4 Subdomain (A2a, A2b, A2c, A2d)	
Restrictive and repetitive behaviour	4 Subdomain (A3a, A3b, A3c, A3d)	4 Subdomain (A2a, A2b, A2c, A2d)
Sensory symptoms	Absent	Present (1 item) out of 4 items in restrictive repetitive behaviour (A2d)
Impairment of daily functional activity	Absent	Present (1 item: Section B, Question 4)
Total number of items	12	9
Diagnosis of ASD	6 out of 12 criteria for diagnosis of autistic disorder	7 out of 9 criteria needed for diagnosis of ASD

DSM: Diagnostic statistical manual; INDT: International Clinical Epidemiology Network tool for autism spectrum disorder; ASD: Autism spectrum disorder; AIIMS: All India Institute of Medical Sciences

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tool on patients. Pilot testing was done in 20 subjects (aged 1–14 years) who were already diagnosed with ASD (based on DSM-5 criteria) in the preceding three months. Internal consistency of items as a whole construct was good with Cronbach alpha 0.92 (individual Cronbach alpha ranging from 0.81–0.89). The inter-rater reliability of tool was very good, and kappa was observed to be 0.95 (95% confidence interval (CI) = 0.85, 1.00).

Study enrollment

Eligible children attending pediatric outpatient unit were screened consecutively for presence of "suspected ASD" by questioning caregivers for presence of any of the four screening criteria. Those who screened positive were invited to participate in the study. Written informed consent was obtained from parent/ guardian of every child participating in the study. INDT-ASD tool and Developmental profile-3 (DP-3, to assess developmental quotient(DQ)) [7] were administered by Investigator 1. Subsequently, CARS and AIIMS modified INDT-ASD tool were administered by Investigators 2 and 3. The sequence of administration was CARS (Investigator 2) followed by AIIMS modified INDT-ASD tool (Investigator 3) in one group and in another group, AIIMS modified INDT-ASD tool (Investigator 2) followed by CARS (Investigator 3). This sequence was adopted to minimize rating bias. Study subjects were finally evaluated independently by a team of experts (Gold standard/Investigator 4). Each evaluator was blinded to original diagnosis and assessment results of other evaluator; their evaluations were separately sealed in opaque envelops immediately after assessment. Study flow is illustrated in Fig 1.

Gold standard assessment was performed by a team consisting of three members: one paediatric neurologist, one clinical psychologist and one child psychiatrist. Expert review was based on history and observation of the child for possible fulfilment of DSM-5 criteria and final diagnosis was categorized as presence or absence of ASD. Patient's treatment and management plan were guided by assessment done by the team of experts. A consensus of diagnosis was reached among team members after a round table discussion. If there was a discrepancy on more than two clinical features, the study participant was reassessed next day by a different set of team members. In case of persistent discordance, all members of gold standard assessment team reached a consensus diagnosis by discussion.

Statistical analysis

Sensitivity, specificity, positive and negative predictive value of AIIMS modified INDT-ASD tool was calculated by comparison with DSM-5 based expert diagnosis. Correlation between severity as per this tool and by CARS was assessed using Pearson correlation. Receiver Operating Characteristics (ROC) curve was used to determine the cut off score for diagnosis and for cut off score (as compared to CARS score) to diagnose severe ASD. STATA version 13.0 was used for statistical analysis.

Results

Two-hundred-twenty-five children were enrolled (159 (70.7%) males). None refused consent to participate. The median (IQR) age of study cohort was 47 (36, 63.5) months. The baseline characteristics of cohort have been illustrated in Table 2. One-hundred-twenty-eight (56.9%) of 225 enrolled children were diagnosed as ASD based on gold standard assessment. Overall, nearly 51% children had development quotient (DQ) $\leq$50. The proportion of children with DQ$\leq$50 was significantly higher among children with ASD (60.2%) than those without ASD (39.2%, p = 0.002). Thirteen (5.7%) children (nine males) were in age group of 1–2 years. The median age of the $\leq$2years subgroup was 18months (15-24months). One of the thirteen

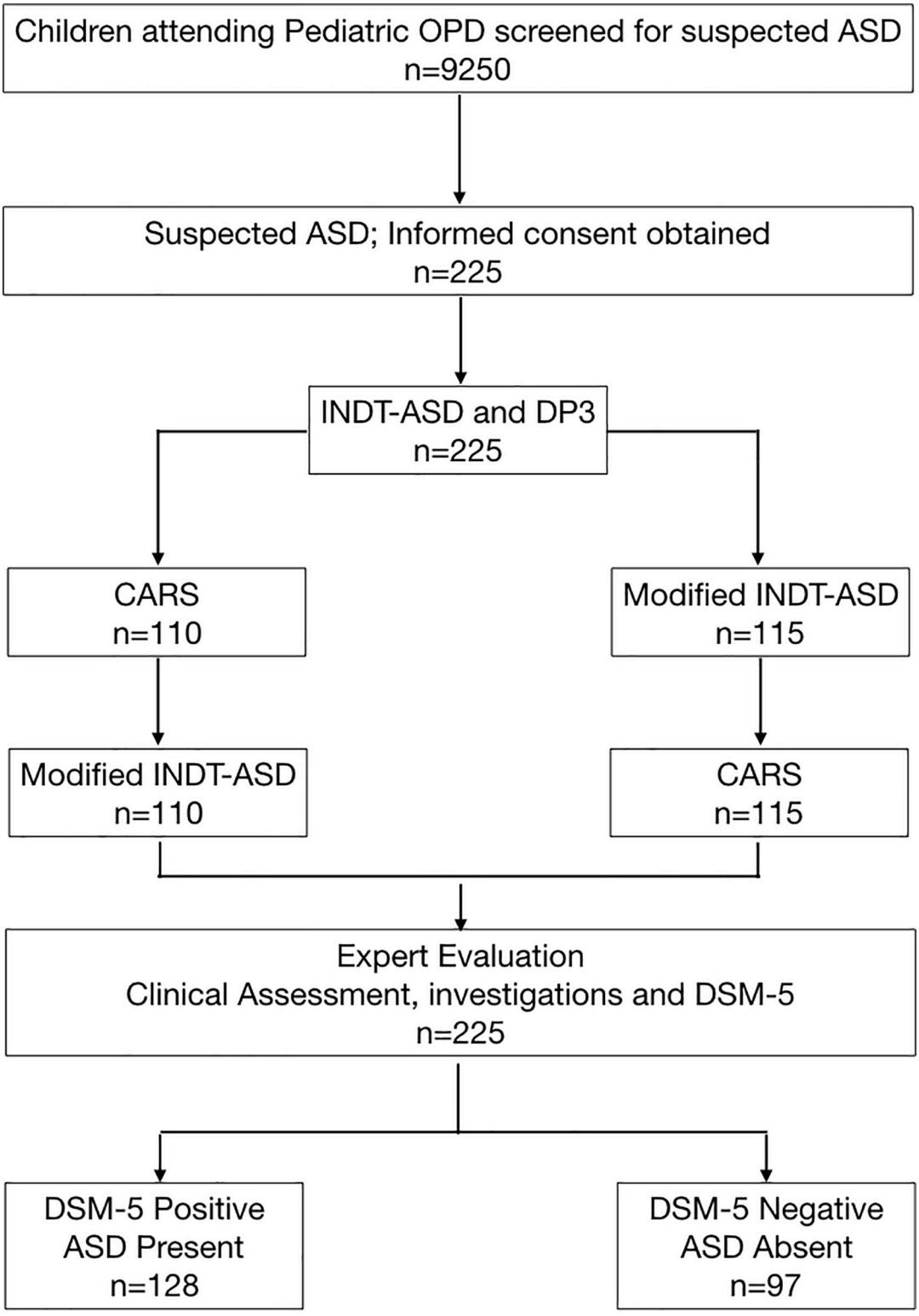

Fig 1. Flow of patients.

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Table 2. Baseline data.

Variable	Complete Cohort n = 225	ASD +ve by DSM n = 128	ASD–ve by DSM n = 97
Age (months)			
Mean ± SD	54.59±29.14	58.58±31.15	49.33±5.47
Median	47	49	44
IQR	36–63.50	37–74	32.50–53.50
Range	15–180	22–180	15–146
Gender, N(%)			
Males	159 (70.7%)	99 (77.3%)	60 (61.9%)
Development Quotient, N(%)			
≤50	115 (51.1%)	77 (60.2%)	38 (39.2%)
51–60	64 (28.4%)	43 (33.6%)	21 (21.6%)
61–70	33 (14.7%)	5 (3.9%)	28 (28.9%)
71–80	8 (3.6%)	2 (1.6%)	6 (6.2%)
81–90	2 (0.9%)	0	2 (2.1%)
>90	3 (1.3%)	1 (0.8%)	2 (2.1%)
CARS Score, N(%)			
No autism (<30)	106 (47.1%)	11 (8.6%)	95 (97.9%)
Mild to Moderate (30–36.5)	39 (17.3%)	37 (28.9%)	2 (2.1%)
Severe (≥37)	80 (35.6%)	80 (62.5%)	0

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children, in the age group ≤2years, was ASD positive by DSM-5 and he also tested positive by the tool.

Diagnostic performance of AIIMS modified INDT-ASD tool against gold standard DSM-5 based expert diagnosis revealed sensitivity (95% CI) and specificity (95% CI) of 98.4% (94.5%-99.8%) and 91.7% (84.4%-96.4%), respectively (Table 3). Pearson correlation between diagnosis based on CARS and the modified tool for ASD was 0.76 ($p<0.01$) (Table 4).

The modified tool was false positive in 8 of 97 cases (8.2%). The final diagnosis of false positive cases included- Intellectual Disability (ID- 6) and Social Communication Disorder (SCD-2). Similarly, numbers of cases that were falsely diagnosed as 'no ASD' by tool were two out of 128 (1.55). Both cases were down by one criterion among stringent 3 out 3 criteria in section A1.

A score of ≥10 on this tool diagnosed ASD with sensitivity and specificity of 92.97% and 92.98% respectively (AUC = 0.98). The cut-off score to diagnose moderate ASD (CARS score

Table 3. AIIMS modified INDT-ASD tool validation statistics as compared to gold standard (DSM-5).

	Gold standard (DSM-5 based expert diagnosis)		Total cases
	ASD present (n = 128)	ASD absent (n = 97)	
AIIMS modified INDT ASD tool: ASD **present**	126	8	134
AIIMS modified INDT ASD tool: ASD **absent**	2	89	91
	128	97	225

a. Sensitivity: 98.44% [94.47% to 99.81%]
b. Specificity: 91.75% (84.39% to 96.37%)
c. Positive Predictive Value: 94.03% (88.58% to 97.39%)
d. Negative Predictive Value: 97.80% (92.29% to 99.73%)

AIIMS: All India Institute of Medical Sciences; INDT: International Clinical Epidemiology Network tool for autism spectrum disorder; ASD: Autism spectrum disorder; DSM: Diagnostic statistical manual of mental disorders

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Table 4. Diagnostic performance of AIIMS modified INDT ASD tool across Childhood Autism Rating Scale (CARS) severity.

CARS Severity	Tool Positive	Tool Negative
Non autistic (CARS<30) (n = 106)	11 (10.4%)	95 (89.6%)
Mild to moderate (CARS = 30–36.5) (n = 39)	37 (94.9%)	2 (5.1%)
Severe (CARS>36.5) (n = 80)	80 (100%)	0

AIIMS: All India Institute of Medical Sciences; INDT: International Clinical Epidemiology Network tool for autism spectrum disorder; ASD: Autism spectrum disorder; DSM: Diagnostic statistical manual of mental disorders

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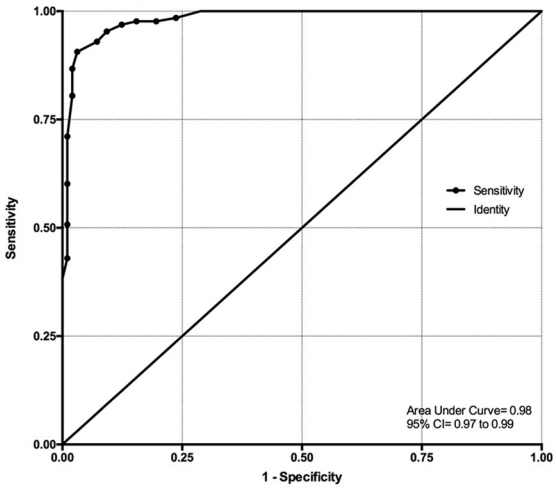
34 to 36.5) was ≥11 with sensitivity and specificity of 90.76% and 89.62% respectively (AUC = 0.93). Similarly, the cut-off score for diagnosing severe ASD was ≥14, which corresponded to CARS score of >36.5. At this cut-off, the sensitivity and specificity were determined to be 80% and 80.69% respectively (AUC = 0.89) (Fig 2).

Discussion

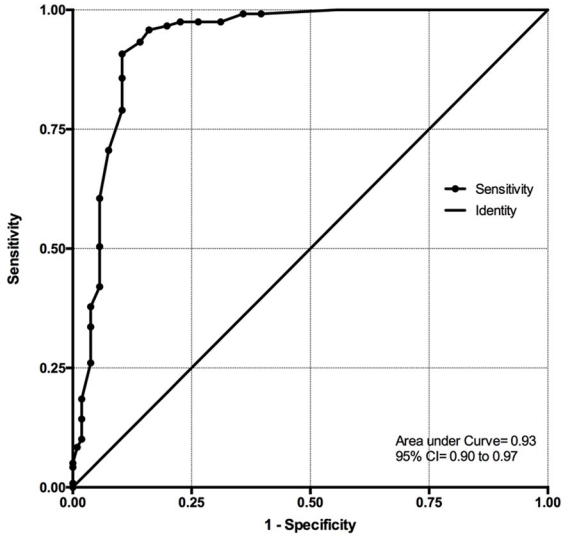
We demonstrate that DSM-5 based AIIMS modified INDT-ASD tool has good psychometric properties for diagnosis of ASD. In our cohort, the tool demonstrated a sensitivity and specificity of 98.4% (95% CI = 94.5%-99.8%) and 91.7% (95% CI = 84.4%-96.4%), respectively. The modified tool had false positivity of 8.2%, while false negative rate was 1.55%. These properties are also supported by its correlation with severity on CARS; with a score of ≥14 on this tool predicts severe ASD with sensitivity and specificity of almost 80% each.

DSM-5, currently constitutes the standard criteria available for ASD diagnosis. Various tools that are available for diagnosis of ASD are DSM-IV or ICD-10 based. Currently, 'gold standard' diagnosis of ASD is a protracted and time-consuming process that requires a qualified multi-disciplinary team to assess behavioral and parent-report information. Considering the relative inaccessibility of LMICs to gold standard for ASD diagnosis and also the expense involved with some of the tools, it is essential to freely adapt, translate and validate diagnostic tools as needed for use in diverse cultures and settings. INDT-ASD tool was an attempt in this direction and it facilitated ASD diagnosis by using appropriateness criteria developed for Indian context. The INDT-ASD tool had sensitivity of 98% and specificity of 95.1% against DSM-IV diagnosis of autism[5]. With the transition from DSM-IV to DSM-5, we modified the existing INDT-ASD tool to incorporate the DSM-5 based questions. The AIIMS modified INDT-ASD tool, thus generated, has also shown good diagnostic accuracy. To the best of our knowledge, this is the first DSM-5 based diagnostic tool for ASD in children. Considering the incorporation of DSM-5 criteria for diagnosis, expansion of age range to 1–14 years and comparable psychometric properties, present tool can replace the previous tool for ASD diagnosis.

As per the evidence, ADI-R and ADOS are considered the best tools for ASD diagnosis with correct classification rates (as per DSM-IV) of up to 80.8%[8]. Few studies using combined ADOS and ADI-R ratings show that this combination has stood the test of time even after transition of DSM-IV to DSM-5[9, 10]. In a recent study, Developmental Diagnostic Dimensional Interview-short version (3Di-sv) proved to be a solid basis for a diagnostic tool to build upon (based on DSM-5) with some modifications[11]. Though we do not have a direct comparison between our tool and any of the aforementioned tools, but nonetheless we demonstrate sensitivity and specificity in excess of 90% for the AIIMS modified INDT-ASD tool.



a



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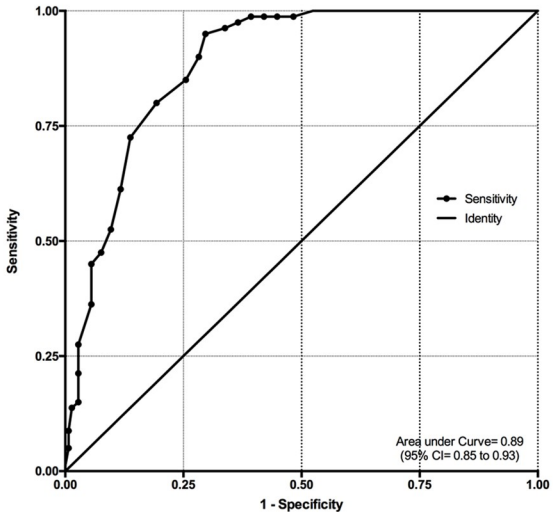

c

Fig 2. Receiver operative characteristics (ROC) curves revealing: (2a) ROC demonstrates that at AIIMS Modified INDT-ASD score of >10, ASD can be diagnosed with sensitivity and specificity of 92.97% and 92.98% respectively

(Area under curve (AUC) = 0.98); (2b) ROC demonstrates that with AIIMS Modified INDT-ASD score of >11, "moderate ASD" (CARS score of 34–36.5) can be diagnosed with sensitivity and specificity of 90.76% and 89.62% respectively (AUC = 0.93); and (2c) ROC demonstrates that with AIIMS Modified INDT-ASD score of >14, "severe ASD" (CARS score>36.5) can be diagnosed with sensitivity and specificity were determined to be 80% and 80.69% respectively (AUC = 0.89).

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ASD as a diagnosis has immense phenotypic heterogeneity in terms of symptom severity, verbal and non-verbal IQ, and social attention[12, 13]. On one end of this spectrum are the children with impaired intellectual capabilities and at the other end are children with autism with average or above average intellectual abilities (high functioning autism)[12]. The elimination of sub-diagnosis in DSM-5 have led to concerns that DSM-5 criteria may underdiagnose ASD and especially impact the Asperger and Pervasive Developmental Disorder (PDD) end of spectrum. Studies have however, indicated that most individuals with a prior DSM-IV PDD meet DSM-5 diagnostic criteria for ASD and SCD[14, 15].

Screening criteria adopted in the present study are one of the objective criteria available in literature, for surveillance of children, to find those who need screening for ASD. Though these screening criteria are dominated by language delay, these may be useful for ASD screening in LMICs where standard screening tools are not available. Extrapolating these criteria for screening children (for broad age-group: 1–14 years) might raise a concern of losing out on children with good verbal abilities and those with high functioning ASD. This concern is similar to that of applying DSM-5 criteria on those diagnosed with ASD based on DSM-IV. This could probably explain the relatively comparable diagnostic performance of DSM-5 based new tool (sensitivity = 97%) with DSM-IV based INDT-ASD tool (sensitivity = 98%). This might also be contributory for majority of enrolled children in present study having a DQ <70.

In the present study, it was observed that six children with ID and two with SCD (median age of 49 months) were labelled as ASD by the tool; thereby, raising a concern of misdiagnosing ID and SCD as ASD. This tool, akin to DSM-5 criteria, renders provision for co-existing diagnosis of ID with ASD and liberty to mark that features of ASD can be explained by ID. Therefore, the final diagnosis might not suffer when test for cognitive abilities are used in conjunction with the tool.

Existing tools for diagnosis of ASD are based on ICD 10 and DSM-IV[5, 16, 17]. Current study developed a well-structured, user-friendly, physician-administered DSM-5 based tool for diagnosis of ASD. This tool is easy to administer and requires minimal training. Good internal consistency of the tool (Cronbach alpha 0.92) demonstrates that symptom cluster of the modified tool was homogenous.

The biggest strength of the study is development of an updated DSM-5 based diagnostic tool to facilitate diagnosis of ASD especially in LMIC which may have limited access to other commercially available tools. In addition, a robust study design, and adequate sample size add to strength of this study. The present study has a few limitations. Firstly, this study lacks concurrent comparison of AIIMS Modified INDT-ASD Tool with ADOS and ADI-R. However, this was beyond the scope of this study. We primarily aimed to modify the existing tool and compare it with DSM-5 and not with other tools. Secondly, there was limited enrollment in the age group of 1 to 2 years. However, we feel that diagnosis of ASD is still evolving in children less than 2 years of age. We still have to identify early markers before we can conclusively diagnose ASD in this population. Thirdly, the applicability in other LMICs needs further evaluation. And finally, its utility as a diagnostic tool for ASD among children suspected with autism might raise a concern considering specificity of 91.7% (84.4%-96.4%) and false positivity rate of 8.2%. However, administration of other diagnostic instruments for cognitive assessment could avert this

concern. Hence, the present tool can become a part of the comprehensive assessment of ASD that consists of an assessment of symptom cluster, cognition, language, and speech.

To conclude, DSM-5 based AIIMS modified INDT-ASD tool has good psychometric properties for diagnosis and for severity rating of ASD among children aged 1–14 years. Hence, the present tool offers simple, physician-administered, diagnostic and severity instrument for ASD among children with "suspected autism".

Supporting information

S1 File. AIIMS modified INDT-ASD tool for diagnosis of autism spectrum disorder.
(PDF)

S2 File. Deidentified dataset.
(XLSX)

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